Access DB# 57792

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Geetha Bansal Examiner #: 73967 Date: 1/8/02
Art Unit: 1642 Phone Number 305 3955 Serial Number: 09/744406
Mail Box and Bldg/Room Location: CM1/8A03 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Allogeneic Cellular Immunogens Useful as Cancer Vac
Inventors (please provide full names): Halpern, Michael S.; England, James M.;

Earliest Priority Filing Date: July 24, 1998

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search

1. a cellular immunogen comprising allogeneic donor cells transfected with a transgene construct wherein the transgene can be a mutant or wild type retroviral oncogene

2. Same as above, but the transgene can be a counterpart to A-KT-2, c-erbB-2, MDM-2, c-myc, c-myb, c-ras, C-Src, c-yes.

3. The donor cells can be fibroblast or bone marrow derived APC's.

Thanks GB

Point of Contact:
Beverly Sheers
Technical Info. Specialist
CM1 1C14 Tel: 308-4994
/EOS

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STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: Beverly 1499	NA Sequence (#)		STN	✓
Searcher Phone #:	AA Sequence (#)		Dialog	
Searcher Location:	Structure (#)		Questel/Orbit	
Date Searcher Picked Up:	Bibliographic		Dr.Link	
Date Completed: 01-17-02	Litigation		Lexis/Nexis	
Searcher Prep & Review Time:	Fulltext		Sequence Systems	
Clerical Prep Time: 12	Patent Family		WWW/Internet	
Online Time: 33	Other		Other (specify)	

PTO-1590 (1-2000)

(FILE 'CAPLUS' ENTERED AT 12:28:35 ON 17 JAN 2002)

L1 8045 SEA FILE=CAPLUS ABB=ON PLU=ON ALLOGEN? AND (CELL OR APC OR ANTIGEN PRESENT? OR FIBROBLAST OR BONE MARROW)

L2 255 SEA FILE=CAPLUS ABB=ON PLU=ON L1 AND (TRANSGEN### OR (AKT OR CERBB OR C(W)(ERBB OR ERB B) OR MDM)(W)2 OR C(W)(MYC OR MYB OR RAS OR SRC OR YES) OR CMYC OR CMYB OR CRAS OR CSRC OR CYES OR AKT2 OR CERBB2 OR C ERBB2 OR MDM2)

L3 19 SEA FILE=CAPLUS ABB=ON PLU=ON L2 AND IMMUNOGEN?

L1 8045 SEA FILE=CAPLUS ABB=ON PLU=ON ALLOGEN? AND (CELL OR APC OR ANTIGEN PRESENT? OR FIBROBLAST OR BONE MARROW)

L2 255 SEA FILE=CAPLUS ABB=ON PLU=ON L1 AND (TRANSGEN### OR (AKT OR CERBB OR C(W)(ERBB OR ERB B) OR MDM)(W)2 OR C(W)(MYC OR MYB OR RAS OR SRC OR YES) OR CMYC OR CMYB OR CRAS OR CSRC OR CYES OR AKT2 OR CERBB2 OR C ERBB2 OR MDM2)

L4 3 SEA FILE=CAPLUS ABB=ON PLU=ON L2 AND ONCOGEN##

L5 21 L3 OR L4

L5 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:922556 CAPLUS

TITLE: Immunological prevention of spontaneous tumors: a new prospect?

AUTHOR(S): Quaglino, Elena; Rovero, Stefania; Cavallo, Federica; Musiani, Piero; Amici, Augusto; Nicoletti, Giordano; Nanni, Patrizia; Forni, Guido

CORPORATE SOURCE: Ospedale San Luigi Gonzaga, Department of Clinical and Biological Sciences, University of Turin, I-10043, Orbassano, Italy

SOURCE: Immunology Letters (2002), 80(2), 75-79
CODEN: IMLED6; ISSN: 0165-2478

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Recent demonstrations of the specific immune prevention of mammary cancer in female BALB/c mice **transgenic** for the rat Her-2/neu **oncogene** (BALB-neuT) have resulted in reconsideration of the immune mechanisms that inhibit tumor growth. All the mammary glands of these mice progress asynchronously, but consistently, from hyperplasia to invasive carcinoma. Overexpression of the **oncogene** product p185neu is first evident in the rudimentary glands of 3-wk-old mice. Carcinogenesis is prevented by vaccination with plasmids coding for the extracellular and transmembrane domains of this p185neu, or with **allogeneic cells** expressing p185neu on their membrane, plus the systemic administration of IL-12. This inhibition is the outcome of a delayed-type hypersensitivity specific for p185neu and the prodn. of anti-p185neu antibodies that restrain the proliferation of tumor **cells** by stripping p185neu from their membrane, whereas cytotoxic T lymphocytes seem devoid of a major role.

L5 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:829528 CAPLUS
TITLE: Combined **allogeneic** tumor **cell** vaccination and systemic interleukin 12 prevents mammary carcinogenesis in HER-2/neu **transgenic** mice
AUTHOR(S): Nanni, Patrizia; Nicoletti, Giordano; De Giovanni, Carla; Landuzzi, Lorena; Di Carlo, Emma; Cavallo, Federica; Pupa, Serenella M.; Rossi, Ilaria; Colombo, Mario P.; Ricci, Cinzia; Astolfi, Annalisa; Musiani, Piero; Forni, Guido; Lollini, Pier-Luigi
CORPORATE SOURCE: Cancer Research Section, Department of Experimental Pathology, University of Bologna, Bologna, I-40126, Italy
SOURCE: Journal of Experimental Medicine (2001), 194(9), 1195-1205
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Transgenic** Balb/c mice expressing the transforming rat HER-2/neu **oncogene** develop early and multifocal mammary carcinomas. Within the first 5 mo of life the tissue-specific expression of HER-2/neu causes a progression in all their 10 mammary glands from atypical hyperplasia to invasive carcinoma. It was previously obsd. that chronic administration of interleukin (IL)-12 increased tumor latency, but every mouse eventually succumbed to multiple carcinomas. A significant improvement in tumor prevention was sought by administering **allogeneic** mammary carcinoma **cells** expressing HER-2/neu combined with systemic IL-12. This treatment reduced tumor incidence by 90% and more than doubled mouse lifetime. For the max. prevention p185neu antigen must be expressed by **allogeneic cells**. IL-12 treatment strongly increased the **cell** vaccine efficacy. The mammary glands of mice receiving the combined treatment displayed a markedly reduced epithelial **cell** proliferation, angiogenesis, and HER-2/neu expression, while the few hyperplastic foci were heavily infiltrated by granulocytes, macrophages, and CD8+ lymphocytes. Specific anti-HER-2/neu antibodies were produced and a nonpolarized activation of CD4+ and CD8+ **cells** secreting IL-4 and interferon (IFN)-.gamma. were evident. A central role for IFN-.gamma. in the preventive effect was proven by the lack of efficacy of vaccination in IFN-.gamma. gene knockout HER-2/neu **transgenic** Balb/c mice. A possible requirement for IFN-.gamma. is related to its effect on antibody prodn., in particular on IgG2a and IgG2b subclasses, that were not induced in IFN-.gamma. knockout HER-2/neu mice. In conclusion, our data show that an **allogeneic** HER-2/neu-expressing **cell** vaccine combined with IL-12 systemic treatment can prevent the onset of genetically detd. tumors.
REFERENCE COUNT: 33
REFERENCE(S):
(1) Allione, A; Cancer Res 1994, V54, P6022 CAPLUS
(2) Amici, A; Cancer Immunol Immunother 1998, V47, P183 CAPLUS
(3) Beatty, G; J Immunol 2000, V165, P5502 CAPLUS
(4) Boggio, K; Cancer Res 2000, V60, P359 CAPLUS

(5) Boggio, K; J Exp Med 1998, V188, P589 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:575650 CAPLUS
TITLE: Adenovector-induced expression of human-CD40-ligand (hCD40L) by multiple myeloma **cells**. A model for immunotherapy
AUTHOR(S): Dotti, G.; Savoldo, B.; Takahashi, S.; Goltsova, T.; Brown, M.; Rill, D.; Rooney, C.; Brenner, M.
CORPORATE SOURCE: Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX, USA
SOURCE: Exp. Hematol. (N. Y., NY, U. S.) (2001), 29(8), 952-961
CODEN: EXHMA6; ISSN: 0301-472X
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CD40L restores the **antigen-presenting cell** (**APC**) function of some B-**cell** tumors and induces professional **APC** maturation. We therefore evaluated the effects of **transgenic** CD40L expression on the behavior and **immunogenicity** of human multiple myeloma (MM) **cells**.CD40L expression was induced in a CD40+ (RPMI 8226) and a CD40- (U266B1) human myeloma **cell** line (HMCL) by adenoviral vector gene transfer. The viability and proliferative activity of control HMCL and HMCL/CD40L were detd. by daily trypan blue staining and methyl-3H-thymidine incorporation. Mixed lymphocyte reaction (MLR) with **allogeneic** mononuclear **cells** (MNCs) and coculture of **allogeneic** dendritic **cells** (DCs) with HMCL expressing **transgenic** CD40L were used to evaluate the **APC** function of modified HMCL as well as the role of bystander DCs in inducing an anti-tumor immune response.CD40L expression significantly inhibited the growth of the CD40+ HMCL and induced apoptosis. These effects were less evident for the CD40- HMCL. There was no upregulation of costimulatory mols. on either HMCL following CD40L expression. Both HMCL expressing **transgenic** CD40L induced maturation of bystander DCs and enhanced their ability to stimulate the proliferation of MNCs. DCs cultured with the poorly **immunogenic** RPMI 8226 expressing CD40L upregulated T-lymphocyte release of IFN-.gamma. and other Th1 cytokines (interleukin-2, tumor necrosis factor-.alpha.).Our data suggest that **transgenic** expression of CD40L exerts a dual effect favoring generation of an immune response to human MM. Where the tumor **cells** are CD40+, the engagement of CD40 antigen by CD40L on tumor **cells** induces their apoptosis, allowing uptake of tumor-assocd. antigen by professional **APC**. Independently of tumor-**cell** expression of CD40, **transgenic** expression of CD40L on tumor **cells** allows them to stimulate CD40+ **APC**, to increase their maturation and their capacity to stimulate cytotoxic T lymphocytes (CTL) that recognize the tumor-derived antigens the **APC** may have engulfed.
REFERENCE COUNT: 34
REFERENCE(S): (1) Albert, M; J Exp Med 1998, V188, P1359 CAPLUS
(2) Albert, M; Nature 1998, V392, P86 CAPLUS

(6) Caux, C; J Exp Med 1994, V180, P1263 CAPLUS
(7) Chen, L; Cell 1992, V71, P1093 CAPLUS
(8) Dilloo, D; Blood 1997, V90, P1927 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:282388 CAPLUS
DOCUMENT NUMBER: 135:60111
TITLE: UVB-irradiated dendritic **cells** are impaired in their **APC** function and tolerize primed Th1 **cells** but not naive CD4+ T **cells**
AUTHOR(S): Denfeld, Ralf W.; Hara, Hisamichi; Tesmann, Jens P.; Martin, Stefan; Simon, Jan C.
CORPORATE SOURCE: Department of Dermatology, Albert-Ludwigs-Universitat, Freiburg, 79104, Germany
SOURCE: J. Leukocyte Biol. (2001), 69(4), 548-554
CODEN: JLBIE7; ISSN: 0741-5400
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have shown that low-dose UVB radiation converts Langerhans **cells** (LC) from **immunogenic** to tolerogenic **APC**. Therefore, we questioned whether low-dose UVB irradn. of **bone marrow**-derived dendritic **cells** (DC) alters their **APC** function, thereby inducing tolerance in T **cells**. To address this issue, cocultures of DC; and naive, **allogeneic** T **cells**; naive, OVA-specific TCR-**transgenic** T **cells** from DO11.10 mice; or primed, antigen-specific T **cells** using the Th1 clone AE7 were analyzed. First, we found low-dose UVB-irradiated DC (UVB-DC) to dose-dependently (50-200 J/M2) inhibit T-**cell** proliferation of naive and primed T **cells**. In addn., supernatants harvested from cocultures of UVB-DC and naive T **cells** showed markedly reduced levels of IL-2 and IFN-.gamma. and to a lesser degree of IL-4 and IL-10, suggesting a preferential down-regulation of Th1 responses by UVB-DC. FACS anal. of UVB-DC revealed no changes in surface expression of MHC, costimulatory, and adhesion mols. To test tolerance induction, allo- or antigen-specific T **cells** isolated from cocultures with unirradiated DC and UVB-DC were restimulated with unirradiated DC or IL-2. It is interesting that UVB-DC induced antigen-specific tolerance in the Th1 clone AE7. In contrast, UVB-DC induced a partial inhibition of **allogeneic** T-**cell** proliferation but no tolerance with similar unresponsiveness to restimulation with IL-2 and unirradiated DC irresp. of their haplotype. Similar observations were made when naive, TCR-**transgenic** T **cells** from DO11.10 mice were used. In conclusion, UVB-DC are impaired in their **APC** function and tolerize the primed antigen-specific Th1 clone AE7 but not naive allo- or OVA-specific T **cells**.
REFERENCE COUNT: 24
REFERENCE(S): (1) Banchereau, J; Nature 1998, V392, P245 CAPLUS
(2) Beissert, S; J Investig Dermatol Symp Proc 1999, V4, P61 CAPLUS
(4) Denfeld, R; Photochem Photobiol 1998, V67,

P554 CAPLUS
(5) Elmets, C; J Exp Med 1983, V158, P781 CAPLUS
(6) Hart, D; Blood 1997, V90, P3245 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:8047 CAPLUS
DOCUMENT NUMBER: 135:151248
TITLE: Simultaneous expression of different **immunogenic** antigens in acute myeloid leukemia
AUTHOR(S): Greiner, J.; Ringhoffer, M.; Simikopinko, O.; Szmaragowska, A.; Huebsch, S.; Maurer, U.; Bergmann, L.; Schmitt, M.
CORPORATE SOURCE: Third Department of Medicine, University of Ulm, Ulm, Germany
SOURCE: Exp. Hematol. (N. Y.) (2000), 28(12), 1413-1422
CODEN: EXHMA6; ISSN: 0301-472X
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Identification of **immunogenic** leukemia-assocd. antigens as target structures is mandatory for specific immunotherapy of leukemia. Here, the authors define acute myeloid leukemia (AML) antigens eliciting a humoral immune response in the autologous host. They applied the method of serol. screening of cDNA expression libraries with autologous serum (SEREX). To date, this technique has been used to characterize antigen structures in solid tumors. The mRNA expression pattern of these newly in AML isolated antigens and previously described leukemia antigens (PRAME, MAGE-1, and Wt-1) was evaluated by reverse transcriptase polymerase chain reaction. For Wt-1, Western blotting also was performed. Screening of a cDNA expression library prepd. from a patient with AML FAB M2 using autologous and **allogeneic** sera, followed by sequencing of pos. clones, yielded 3 autoantigens (Prp1p/Zer1p, L19H1, and one without homol. to previously described genes) and 2 antigens reactive with **allogeneic** sera (MAZ, PINCH). PRAME mRNA was expressed in 47% of 34 AML patients, but not in 13 CD34+ **cell** samples or in peripheral blood mononuclear **cells** of 13 healthy volunteers. MRNA expression of MAZ was detected in 44% of AML patients, but only in 8% of healthy donors. Humoral responses to MAZ were detected in 35%. More than 80% of the screened AML patients showed simultaneous expression of .gtoreq.2 of these antigens. Differential expression in AML patients vs. healthy volunteers suggests that the **immunogenic** antigens PRAME and MAZ are potential candidates for immunotherapy in AML.

REFERENCE COUNT: 35
REFERENCE(S):

(1) Berchuck, A; J Soc Gynecol Investig 1994, V1, P181 CAPLUS
(2) Bergmann, L; Blood 1997, V90, P1217 CAPLUS
(3) Bergmann, L; Exp Hematol 1995, V23, P1574 CAPLUS
(4) Bossone, S; Proc Natl Acad Sci 1992, V89, P7452 CAPLUS
(5) Brossart, P; Cancer Res 1998, V58, P732 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:592282 CAPLUS
DOCUMENT NUMBER: 134:113858
TITLE: Spontaneous mammary carcinomas fail to induce an immune response in syngeneic FVBN202 NEU **transgenic** mice
AUTHOR(S): Kurt, Robert A.; Whitaker, Rachel; Baher, Anjelo; Seung, Steven; Urba, Walter J.
CORPORATE SOURCE: Laboratory of Cellular Immunology, Robert W. Franz Cancer Research Center, Providence Portland Medical Center, Oregon Cancer Center, Earle A. Chiles Research Institute, Portland, OR, USA
SOURCE: Int. J. Cancer (2000), 87(5), 688-694
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB FVBN202 mice, which are **transgenic** for the rat neu gene, spontaneously develop mammary carcinomas between 6 and 7 mo of age. We investigated whether these spontaneous tumors (spontaneous breast carcinoma **cells**, SBCC) could elicit an immune response in naive 6- to 8-wk-old FVBN202 **transgenic** and FVBN nontransgenic mice. After s.c. injection of SBCC, the recently activated T **cells**, which were identified by their reduced expression of CD62L (L-selectin), were isolated from the draining lymph nodes, expanded with anti-CD3 and IL-2, and their cytokine response to tumor **cells** in vitro was analyzed. Tumor-vaccine draining lymph node lymphocytes (TVDLN) from **transgenic** mice failed to make IFN-.gamma. in response to the tumor **cells**. However, TVDLN from the nontransgenic mice exhibited a tumor-specific IFN-.gamma. response against the SBCC. This indicates that the SBCC are **immunogenic**. The lack of response in **transgenic** mice could not be attributed to cytokine immune deviation or T-**cell** signaling defects. Although **transgenic** mice were tolerant to their own tumors, their immune competence was established by their ability to respond in an **allogeneic** mixed lymphocyte reaction, to reject an **allogeneic** breast carcinoma **cell** line, and to produce a tumor-specific IFN-.gamma. response against a syngeneic cancer **cell** line. This **transgenic** mouse model provides the opportunity to investigate the immune response against a primary tumor **cell** culture rather than **cell** lines or clones and should prove useful for developing immunotherapies that overcome tolerance to self-tumor antigens.
REFERENCE COUNT: 18
REFERENCE(S): (1) Amici, A; Cancer Immunol Immunother 1998, V47, P183 CAPLUS
(2) Bakker, A; J Exp Med 1994, V179, P1005 CAPLUS
(3) Boon, T; J Exp Med 1996, V183, P725 CAPLUS
(6) Dubois, N; J Hepatol 1991, V13, P227 CAPLUS
(8) Ganss, R; Cancer Res 1998, V58, P4673 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:543605 CAPLUS

DOCUMENT NUMBER: 133:236788
TITLE: Feasibility of CTLA4Ig gene delivery and expression in vivo using retrovirally transduced myeloid dendritic **cells** that induce alloantigen-specific T **cell** anergy in vitro
AUTHOR(S): Takayama, T.; Morelli, A. E.; Robbins, P. D.; Tahara, H.; Thomson, A. W.
CORPORATE SOURCE: Thomas E Starzl Transplantation Institute and Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, 15213, USA
SOURCE: Gene Ther. (2000), 7(15), 1265-1273
CODEN: GETHEC; ISSN: 0969-7128
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Dendritic **cells** (DC) are highly specialized, **bone marrow** (BM)-derived **antigen-presenting cells** (**APC**) that initiate and regulate immune responses. They provide costimulatory signals (in particular, CD40 and the CD28 ligands CD80 and CD86) necessary for naive T **cell** activation. Functional expression of CD80 and CD86 is blocked by the fusion protein cytotoxic T lymphocyte antigen 4-Ig (CTLA4Ig), that promotes tolerance induction in animals. Here, replicating mouse (B10; H2b) myeloid DC progenitors, were retrovirally transduced to express CTLA4Ig using the centrifugal enhancement method. Gene product was detected by immunocyto- or histochem. Maximal DC transduction efficiency was 62%. Compared with control, zeomycin-resistance gene (Zeo)-transduced DC, CTLA4Ig-expressing **cells** showed markedly impaired capacity to stimulate naive **allogeneic** (C3H; H2k) T **cell** proliferation and cytotoxic T lymphocyte (CTL) generation. Their ability to induce alloantigen-specific T **cell** hyporesponsiveness was reversed by exogenous IL-2 in secondary mixed leukocyte reactions (MLR). Following local (s.c.) transfer to **allogeneic** recipients, the genetically modified DC trafficked to T **cell** areas of draining lymphoid tissue, where **transgene** expression was detected. Ex vivo anal. of proliferative and CTL responses revealed donor-specific inhibition of alloimmune reactivity by the CTLA4Ig-transduced DC. This effect was assocd. with marked inhibition of interferon (IFN)-.gamma. prodn., but significant augmentation of IL-4 and IL-10 secretion. Thus, retroviral transduction of DC permits in vivo delivery of CTLA4Ig to the precise microenvironment where antigen (Ag) presentation occurs. Comparatively non-**immunogenic** retroviral vectors, that allow permanent **transgene** expression in DC, and promote localized delivery of the immunosuppressive **transgene** product, promote immune deviation and Ag-specific T **cell** hyporesponsiveness.
REFERENCE COUNT: 51
REFERENCE(S):
(3) Bahnson, A; J Virol Meth 1995, V54, P131 CAPLUS
(4) Banchereau, J; Nature 1998, V392, P245 CAPLUS
(5) Bell, D; Adv Immunol 1999, V72, P255 CAPLUS
(6) Bluestone, J; Immunity 1995, V2, P555 CAPLUS
(7) Chen, W; J Immunol 1998, V160, P1504 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:119419 CAPLUS
DOCUMENT NUMBER: 132:263830
TITLE: Adenoviral transfer of xenogeneic MHC class I gene results in loss of tumorigenicity and inhibition of tumor growth
AUTHOR(S): Campbell, Islay; Moyana, Terence; Carlsen, Svein; Zheng, Changyu; Xiang, Jim
CORPORATE SOURCE: Departments of Microbiology, Oncology, Saskatoon Cancer Center, University of Saskatchewan, Saskatoon, SK, Can.
SOURCE: Cancer Gene Ther. (2000), 7(1), 37-44
CODEN: CGTHEG; ISSN: 0929-1903
PUBLISHER: Nature America, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The immune system confers protection against a variety of pathogens and contributes to the destruction of neoplastic **cells**. Foreign major histocompatibility complex (MHC) protein serves as a potent stimulus to the immune system. In this report, a mouse H-2Kb gene was introduced into two poorly **immunogenic** tumor **cell** lines, a mouse colonic carcinoma **cell** line, MCA-26 (H-2Kd), and a rat mammalian carcinoma **cell** line, LN-4, in an effort to stimulate tumor rejection. The results showed that the expression of xenogeneic MHC class I antigen completely abolished the LN-4 tumorigenicity in rats, whereas the expression of **allogeneic** MHC class I antigen only partially reduced the MCA-26 tumorigenicity in mice. Rats with tumor regression of LN-4/H-2Kb developed a T helper type 1-dominant response, whereas rats with LN-4 tumor growth developed a T helper type 2-dominant response. The immunized rats that experienced LN-4/H-2Kb tumor regression further developed protective immunity against a subsequent challenge of LN-4 **cells**. This protective immunity was mediated by the LN-4 tumor-specific cellular immune response against both the transduced and the parental LN-4 **cells**. Recombinant adenoviral vectors are highly efficient at in vitro and in vivo gene delivery. The LN4 **cells** transfected with the recombinant adenovirus AdV-H-2Kb in vitro expressed the **cell** surface H-2Kb mol. by fluorescence-activated **cell** sorter anal. Adenovirus-mediated H-2Kb gene transfer in vivo can further significantly inhibit pre-established LN-4 tumors. Those rats with complete tumor regression further developed protective immunity against the subsequent challenge of a parental LN-4 tumor. Therefore, this study indicates that the adenovirus-mediated transfer of xenogeneic MHC class I gene may be an effective alternative to the current protocol of cancer gene therapy in which the **allogeneic** MHC class I gene is used.

REFERENCE COUNT: 34
REFERENCE(S):
(1) Alter, B; J Exp Med 1990, V171, P333 CAPLUS
(2) Calorini, L; Cancer Res 1992, V52, P4036 CAPLUS
(3) Carlsen, S; Cancer Res 1993, V53, P2906 CAPLUS
(4) Chen, S; Cancer Res 1996, V56, P3758 CAPLUS
(5) Cole, G; Proc Natl Acad Sci USA 1987, V84, P8613 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:84650 CAPLUS
DOCUMENT NUMBER: 132:136415
TITLE: **Allogeneic** cellular **immunogens** useful as cancer vaccines
INVENTOR(S): Halpern, Michael S.; England, James M.
PATENT ASSIGNEE(S): Allegheny University of the Health Sciences, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000004927	A1	20000203	WO 1999-US15594	19990708
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9949819	A1	20000214	AU 1999-49819	19990708
EP 1100544	A1	20010523	EP 1999-933855	19990708
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1998-93965 P 19980724
WO 1999-US15594 W 19990708

AB A cellular **immunogen** is provided for immunizing a host against the effects of the product of a target proto-**oncogene**, where the overexpression of the target proto-**oncogene** is assocd. with a malignancy. The cellular **immunogen** comprises **allogeneic** (with respect to the host) **cells** which have been transfected with at least one **transgene** construct comprising a **transgene** cognate to the target proto-**oncogene** and a strong promoter to drive the expression of the **transgene** in the transfected **cells**. The **transgene** encodes a gene product which induces host immunoreactivity to host self-determinants of the product of the target proto-**oncogene** gene. The **transgene** may comprise, for example, wild-type or mutant retroviral **oncogene** DNA cognate to the target proto-**oncogene**; or wild-type or mutant proto-**oncogene** DNA of a species different from the host species. The cellular **immunogen** may be prepd. from **allogeneic** donor **cells**, e.g. skin **fibroblasts**, which are stably or transiently transfected with the **transgene** construct contg. the cognate **transgene**. The donor **cells** transfected with the cognate **transgene** constructs are then inserted into the body of the host to obtain expression of the cognate **transgene** in the host.

REFERENCE COUNT: 1
REFERENCE(S): (1) Baetge; US 5656481 A 1997 CAPLUS

L5 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:628104 CAPLUS
DOCUMENT NUMBER: 131:321268
TITLE: Apoptosis of a human melanoma **cell** line specifically induced by membrane-bound single-chain antibodies
AUTHOR(S): De Ines, Concepcion; Cochlovius, Bjorn; Schmidt, Stefanie; Kipriyanov, Sergey; Rode, Hans-Jurgen; Little, Melvyn
CORPORATE SOURCE: Recombinant Antibody Group, Experimental Therapy and Diagnosis Programme, German Cancer Research Center, Heidelberg, 69120, Germany
SOURCE: J. Immunol. (1999), 163(7), 3948-3956
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CD28 is a key regulatory mol. in T **cell** responses. Ag-TCR/CD3 interactions without costimulatory signals provided by the binding of B7 ligands to the CD28R appear to be inadequate for an effective T **cell** activation. Indeed, the absence of B7 on the tumor **cell** surface is probably one of the factors contributing to the escape of tumors from immunol. control and destruction. Therefore, to increase the **immunogenicity** of tumor **cell** vaccines, the authors have expressed anti-CD3 and anti-CD28 single-chain Abs (scFv) sep. on the surface of a human melanoma SkMel63 **cell** line (HLA-A*0201). A mixt. of **cells** expressing anti-CD3 with **cells** expressing anti-CD28 resulted in a marked activation of **allogeneic** human PBL in vitro. The apparent induction of a Th1 differentiation pathway was accompanied by the proliferation of MHC-independent NK **cells** and MHC-dependent CD8+ T **cells**. PBL that had been cultured together with transfected SkMel63 tumor **cells** were able to specifically induce apoptosis in untransfected SkMel63 **cells**. In contrast, three other tumor **cell** lines expressing HLA-A*0201, including two melanoma **cell** lines, showed no significant apoptosis. These results provide valuable information for both adoptive immunotherapy and the generation of autologous tumor vaccines.
REFERENCE COUNT: 38
REFERENCE(S): (2) Bohlen, H; Cancer Res 1997, V57, P1704 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:619975 CAPLUS
DOCUMENT NUMBER: 132:136352
TITLE: Patterns of immune responses evoked by

allogeneic hepatocytes: Evidence for independent co-dominant roles for CD4+ and CD8+ T-**cell** responses in acute rejection

AUTHOR(S): Bumgardner, Ginny L.; Li, Jiashun; Prologo, J. David; Heininger, Marie; Orosz, Charles G.

CORPORATE SOURCE: Division of Transplantation, Department of Surgery, The Ohio State University Medical Center, Columbus, OH, 43210, USA

SOURCE: Transplantation (1999), 68(4), 555-562
CODEN: TRPLAU; ISSN: 0041-1337

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This is the first in a series of reports that characterizes immune responses evoked by **allogeneic** hepatocytes using a functional model of hepatocyte transplantation in mice. "Donor" hepatocytes expressing the **transgene** human alpha-1-antitrypsin (hA1AT-FVB/N, H2q) were transplanted into C57BL/6 (H2b) or MHC II knockout (H2b) hosts treated with anti-CD4, anti-CD8, or a combination of anti-CD4 and anti-CD8 monoclonal antibodies (mAbs). Hepatocyte rejection was detd. as a loss of circulating ELISA-detectable **transgene** product (hA1AT). In addn., some C57BL/6 mice underwent transplantation with FVB/N heterotopic cardiac allografts and were treated with anti-CD4 mAb. Cardiac allograft rejection was detd. by palpation. Graft recipients were tested for donor-reactive alloantibodies and donor-reactive delayed-type hypersensitivity (DTH) responses. The median survival time (MST) of **allogeneic** hepatocytes in normal C57BL/6 mice was 10 days (no treatment), 10 days (anti-CD4 mAb), 14 days (anti-CD8 mAb), and 35 days (anti-CD4 and anti-CD8 mAbs). The MST of hepatocytes in B6 MHC class II knockout mice was 10 days (no treatment) and 21 days (anti-CD8 mAb). The MST of cardiac allografts was 11 days (no treatment) and > 100 days (anti-CD4 mAb). Donor-reactive DTH responses were readily detected in both untreated and mAb-treated recipients. Donor-reactive alloantibody was barely detectable in untreated hosts. These studies demonstrate that **allogeneic** hepatocytes are highly **immunogenic** and stimulate strong **cell**-mediated immune responses by both CD4+ and CD8+ T **cells**, even when treated with agents that can cause acceptance of cardiac allografts. Indeed, CD4+ or CD8+ T **cells** seem to independently cause hepatocellular allograft rejection. **Allogeneic** hepatocytes evoked strong donor-reactive DTH responses but were poor stimuli for donor-reactive antibody prodn. This is an unusual pattern of immune reactivity in allograft recipients.

REFERENCE COUNT: 40

REFERENCE(S):
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(10) Chen, Z; Eur J Immunol 1992, V22, P805 CAPLUS
(14) Grusby, M; Science 1991, V253, P1417 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:613583 CAPLUS
DOCUMENT NUMBER: 131:227662
TITLE: Enhancement of immune response to tumor antigens
INVENTOR(S): Kaplan, Johanne; Gregory, Richard J.
PATENT ASSIGNEE(S): Genzyme Corporation, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9946992	A1	19990923	WO 1999-US6039	19990319
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9931029	A1	19991011	AU 1999-31029	19990319
EP 1071333	A1	20010131	EP 1999-912716	19990319
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1998-78889 P 19980320
WO 1999-US6039 W 19990319

AB This invention provides methods and compns. for breaking tolerance to a self-antigen, esp. in the context of a tumor-assocd. antigen. In one embodiment, dendritic **cells** are transduced to express tumor antigens derived from **allogeneic** or heterologous species to break immunol. tolerance and induce a cross-reactive immune response against the corresponding native or self-antigen.

REFERENCE COUNT: 8
REFERENCE(S):
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(6) Pachner, A; Immunol Lett 1989, V20(3), P199 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:473657 CAPLUS
DOCUMENT NUMBER: 132:11461
TITLE: Xenogeneic and **allogeneic** anti-MHC immune responses induced by plasmid DNA immunization
AUTHOR(S): Cruz, Charles S. Dela; Chamberlain, John W.; MacDonald, Kelly S.; Barber, Brian H.
CORPORATE SOURCE: Department of Immunology, University of Toronto, Toronto, ON, M5S 1A8, Can.
SOURCE: Vaccine (1999), 17(20-21), 2479-2492
CODEN: VACCDE; ISSN: 0264-410X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Major histocompatibility complex (MHC) proteins are known to be incorporated into the human immunodeficiency virus (HIV-1) envelope as the virion buds from the host **cell** surface. Studies using simian immunodeficiency virus (SIV) infection of macaques have demonstrated that immunization with uninfected human **cells** or purified HLA proteins can provide protection from challenge with live SIV when it is grown in human **cells** expressing the same MHC alleles. Thus the induction of anti-MHC immune responses represents an important option to consider with respect to vaccine design for SIV and HIV. Here we examine plasmid DNA immunization strategies as an alternative to cellular or protein **immunogens** for the induction of xenogeneic and **allogeneic** immune responses in C57BL/6 mice and in an HLA **transgenic** mouse model system, resp. We compared the **immunogenicity** of HLA-A2- and HLA-B27-expressing splenocytes with the corresponding plasmid DNA **immunogens**. Results from the **transgenic** mouse expts. indicate that plasmid DNA immunization with both class I and class II MHC-encoding vectors can elicit antibody responses recognizing conformationally intact MHC mols. Our data also show that immunization with class I MHC-encoding DNA **immunogens** can elicit cytotoxic T-lymphocyte responses, demonstrating the potential to mobilize both antibody and **cell**-mediated anti-MHC immune responses in the context of this approach to HIV-1 vaccine design.

REFERENCE COUNT: 49

REFERENCE(S):
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(2) Arthur, L; Science 1992, V258, P1935 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:186810 CAPLUS
DOCUMENT NUMBER: 131:30937
TITLE: Induction of **immunogenicity** of a human renal-**cell** carcinoma **cell** line by TAP1-gene transfer
AUTHOR(S): Kallfelz, Michael; Jung, Dirk; Hilmes, Christine; Knuth, Alexander; Jaeger, Elke; Huber, Christoph; Seliger, Barbara
CORPORATE SOURCE: Johannes Gutenberg-Universitat, III. Medizinische Klinik, Mainz, 55101, Germany
SOURCE: Int. J. Cancer (1999), 81(1), 125-133
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Reduced expression of the major histocompatibility complex (MHC) class I antigens has been demonstrated in renal-**cell** carcinoma (RCC), and appeared to be assocd. with deficiencies in the expression and function of different components of the MHC-class-I-antigen-processing pathway and poor recognition by cytotoxic T-lymphocytes (CTL). To investigate the role of peptide transporters for the **immunogenic** phenotype of RCC, tumor **cells** were stably transfected with the human TAP1A gene.

While the TAP1 transfectants showed heterogeneous TAP1-**transgene** expression pattern of mRNA and protein, high TAP1 expression and a TAP-controlled increase in MHC-class-I surface expression could be achieved in selected transfectants. IFN-.gamma. up-regulates the expression of MHC-class-I antigens and TAP1 both in control and in TAP1-transfected RCC **cells** to a similar level. No additive effect of TAP1 over-expression was obsd. in TAP1 transfectants. Although no enhanced CTL-mediated lysis was obtained, cytokine release was substantially increased in response to TAP1-transfected RCC **cells**, but not to control **cells**. Furthermore, TAP1 transfectants were able to stimulate the proliferation of **allogeneic** T **cells** . These studies suggest that abnormalities of MHC-class-I surface expression due to dysfunctional peptide transporters contribute to the immune escape phenotype of RCC **cells** and that the immune tolerance of RCC could be altered by TAP1-gene transfer.

REFERENCE COUNT: 25
REFERENCE(S):
(1) Androlewicz, M; Proc nat Acad Sci (Wash) 1993, V90, P9130 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:542991 CAPLUS
DOCUMENT NUMBER: 129:160641
TITLE: Cancer immunotherapy with semi-**allogeneic cells**
INVENTOR(S): Cohen, Edward P.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 120 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9833527	A2	19980806	WO 1998-US1824	19980130
WO 9833527	A3	19981105		
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1012240	A2	20000628	EP 1998-904782	19980130
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL, IE				
US 6187307	B1	20010213	US 1998-16528	19980130
JP 2001522226	T2	20011113	JP 1998-533112	19980130

PRIORITY APPLN. INFO.: US 1997-36620 P 19970131
WO 1998-US1824 W 19980130

AB The present invention relates to improved semi-**allogeneic immunogenic cells** which act to stimulate and

induce an immunol. response when administered to an individual. In particular, it relates to **cells** which express both **allogeneic** and syngeneic MHC determinants and which also express at least one antigen recognized by T lymphocytes. The invention is also directed to methods of inducing an immune response and methods of treating tumors by administering the semi-**allogeneic immunogenic cells** to an individual.

L5 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:353653 CAPLUS
DOCUMENT NUMBER: 129:160357
TITLE: Characterization of human colon cancer antigens recognized by autologous antibodies
AUTHOR(S): Scanlan, Matthew J.; Chen, Yao-Tseng; Williamson, Barbara; Gure, Ali O.; Stockert, Elisabeth; Gordan, John D.; Tuireci, Ozlem; Sahin, Ugur; Pfreundschuh, Michael; Old, Lloyd J.
CORPORATE SOURCE: New York Branch at Memorial Sloan-Kettering Cancer Center, Ludwig Institute for Cancer Research, New York, NY, 10021, USA
SOURCE: Int. J. Cancer (1998), 76(5), 652-658
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The screening of cDNA expression libraries derived from human tumors with autologous antibody (SEREX) has proven to be a powerful method for defining the structure of tumor antigens recognized by the humoral immune system. In the present study, 48 distinct antigens (NY-CO-1-NY-CO-48) reactive with autologous IgG were identified by SEREX anal. in 4 patients with colon cancer. Sequencing anal. showed that 17 of the cDNA clones were previously uncharacterized mols. and 31 represented known gene products. The individual cDNA clones were analyzed in the following manner: a search for mutations or other structural changes; an anal. of mRNA expression in a panel of normal tissues; and a frequency anal. of the antibody response to the expressed product in the sera of colon cancer patients and normal individuals. The initial anal. showed NY-CO-13 to be a mutated version of the p53 tumor suppressor gene. Three of the 48 antigens showed a differential pattern of mRNA expression, with NY-CO-27 (galectin-4) expressed primarily in gastrointestinal tract, and NY-CO-37 and -38 showing a pattern of tissue-specific isoforms. With regard to **immunogenicity**, 20 of the 48 antigens were detected by **allogeneic** sera; 14 of these were reactive with sera from both normal donors and cancer patients, and 6 other clones (NY-CO-8, -9, -13, -16, -20 and -38) reacted exclusively with sera from colon cancer patients (ranging from 14% to 27%). Our results on colon cancer illustrate both the complexity and the potential of the SEREX approach for anal. of the humoral immune response against human cancer.

L5 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:258439 CAPLUS
DOCUMENT NUMBER: 129:26749
TITLE: Enhanced tumor protection by granulocyte-macrophage colony-stimulating factor

expression at the site of an **allogeneic** vaccine

AUTHOR(S): Thomas, Matthew C.; Greten, Tim F.; Pardoll, Drew M.; Jaffee, Elizabeth M.

CORPORATE SOURCE: Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA

SOURCE: Hum. Gene Ther. (1998), 9(6), 835-843
CODEN: HGTHE3; ISSN: 1043-0342

PUBLISHER: Mary Ann Liebert, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Murine tumor models have demonstrated that whole tumor **cell** vaccines engineered to secrete certain cytokines in a paracrine fashion elicit systemic immune responses capable of eliminating small amts. of established tumor. In particular, autologous tumors that express the cytokine GM-CSF induce potent systemic immune responses against poorly **immunogenic** murine tumors. However, phase I clin. trials have demonstrated the tech. difficulty of routinely expanding primary autologous human tumor **cells** to the nos. required for vaccination, making the generalization of autologous vaccines impractical. Dissection of the mechanism by which antitumor immunity is generated has demonstrated that GM-CSF recruits professional **antigen-presenting cells** that act as intermediates in presenting tumor antigen to and activating effector T **cells**. Furthermore, the identification of commonly recognized murine and human tumor antigens indicates that many are shared rather than unique. These findings would suggest that **allogeneic** as well as autologous tumor **cells** can be used as the vaccinating **cells** for activating antitumor immunity. A major concern in the application of **allogeneic** vaccines relates to the potential interference of **allogeneic** MHC expression at the vaccine site with priming of tumor-specific T **cell** responses. Here the authors describe a series of expts. that directly examines the effects of **allogeneic** MHC mols. on the immune-priming capabilities of a whole **cell** tumor vaccine engineered to secrete GM-CSF. The results demonstrate that the expression of an **allogeneic** MHC mol. by a vaccine **cell** can actually enhance the induction of systemic antitumor immunity. In addn., **allogeneic** MHC expression has no inhibitory effect on the ability of GM-CSF-transduced vaccines to induce systemic antitumor immunity. These findings support the design of clin. trials for testing this more feasible and generalizable **allogeneic** whole tumor **cell** vaccine approach.

L5 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:181516 CAPLUS

DOCUMENT NUMBER: 128:293868

TITLE: Resistance to melanoma in mice immunized with semiallogeneic **fibroblasts** transfected with DNA from mouse melanoma **cells**

AUTHOR(S): De Zoeten, Edwin F.; Carr-Brendel, Victoria; Cohen, Edward P.

CORPORATE SOURCE: Dep. of Microbiology and Immunology, University of Illinois at Chicago, Chicago, IL, 60612, USA

SOURCE: J. Immunol. (1998), 160(6), 2915-2922
CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tumor-assocd. Ags (TAA) that characterize a population of malignant **cells** are recognized by CTLs in the context of determinants specified by the MHC class I locus. Nevertheless, most progressively growing neoplasms do not induce antitumor immune responses that can control tumor **cell** growth. The TAA may be insufficiently antigenic. The authors found previously that immunization of mice with a cellular **immunogen** prepd. by transfecting tumor DNA into **allogeneic** mouse **fibroblasts** resulted in strong antitumor immune responses that were specific for the type of tumor from which the DNA was obtained. Since the **fibroblasts** differed at the MHC from the immunized mice, the authors postulated that the **immunogenic** properties of the **allogeneic** transfected **cells** might be enhanced if the **cells** were modified to express syngeneic class I determinants. In a mouse melanoma model system, the H-2Kb gene was introduced into LM mouse **fibroblasts** (H-2k). Afterward, the **cells** were transfected with DNA from B16 melanoma **cells** (H-2b). The transfected **cells** were tested for their immunotherapeutic properties in C57BL/6J mice (H-2b) with melanoma. Mice with melanoma treated solely by immunization with the semiallogeneic transfected **cells** developed strong, long-term resistance to the growth of the tumor. In some instances, the mice survived indefinitely. Intact rather than disrupted transfected **cells** were required to induce the antimelanoma response, consistent with direct presentation of TAA by the transfected **cells**. The augmented resistance to melanoma in mice treated with the semiallogeneic transfected **cells** points toward an analogous form of therapy for cancer patients.

L5 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:60490 CAPLUS
DOCUMENT NUMBER: 124:143026
TITLE: Plasticity of the T **cell** receptor repertoire in TCR .beta.-chain **transgenic** mice
AUTHOR(S): Listman, James A.; Rimm, Ilonna J.; Wang, Yunsheng; Geller, Michelle C.; Tang, J. C.; Ho, Sam; Finn, Patricia W.; Perkins, David L.
CORPORATE SOURCE: Lab. Immunogenetics Transplant., Brigham and Women's Hosp., Boston, MA, 02115, USA
SOURCE: Cell. Immunol. (1996), 167(1), 44-55
CODEN: CLIMB8; ISSN: 0008-8749
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The potential .alpha..beta. T **cell** receptor (TCR) repertoire in normal mice is extremely large and estd. by M. M. Davis and P. J. Bjorkman (1988) to include 5.2 .times. 1018 different receptor mols. This tremendous diversity provides the basis for T **cell** recognition of the universe of antigens including bacterial, viral, and **allogeneic** epitopes. Expression of a single TCR .beta.-chain **transgene** should alter the repertoire by limiting the available diversity, therefore, creating holes in the repertoire or producing TCR with decreased affinity. To det. the effect of drastically decreasing the size of

the repertoire, the authors investigated T **cell** responses in TCR .beta.-chain **transgenic** expressing the V.beta.8.2 **transgene**. Previous results showed that >98% of T **cells** in these mice express the **transgene**; thus, the TCR repertoire is reduced by orders of magnitude. The authors tested the T **cell** responses of the **transgenic** mice and nontransgenic littermates to nine different MHC haplotypes in mixed lymphocyte reactions, five protein antigens, and eight **immunogenic** peptides. Surprisingly the **transgenic** mice responded to all antigenic stimuli tested indicating the lack of a hole in the TCR repertoire. Interestingly, however, the response in every case was quant. lower than the response by the nontransgenic littermates. In contrast **transgenic** and nontransgenic T **cells** responded equiv. to stimulation with mitogens or to stimulation with immobilized .alpha.-TCR mAb indicating that the **transgenic** T **cells** had a normal capacity to respond. To differentiate between decreased TCR affinity and decreased precursor frequency, the authors performed a limiting diln. anal. to the peptide antigens CI:NP and OVA324-339. The results showed approx. a three- to eight-fold decrease in the frequency of **transgenic** T **cells** responding to the peptide compared to nontransgenic littermates. The authors previously showed that the response to cI84-98 and PLP could be blocked with anti-V.beta.8 mAb indicating that V.beta.8.2-bearing T **cells** are capable of responding to peptide antigen. Anal. of TCR V.alpha. chain expression by PCR and flow cytometry showed similar V.alpha. expression in both the **transgenic** and the nontransgenic mice. These results demonstrate tremendous plasticity in the TCR repertoire permitting T **cell** responses by the **transgenic** mice to all antigens tested. However, the decreased magnitude of the responses may impair the capacity to defend against natural pathogens. Therefore, although the large TCR repertoire of normal mice may not be necessary to produce in vitro responses to many exptl. antigens, it may confer survival benefits in natural environments.

L5 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:214593 CAPLUS
DOCUMENT NUMBER: 122:7372
TITLE: Natural killer **cells** recognize common antigenic motifs shared by H-2Dd, H-2Ld and possibly H-2Dr molecules expressed on **bone marrow cells**
AUTHOR(S): Yu, Yik Yeung L.; Forman, James; Aldrich, Carla; Blazar, Bruce; Flaherty, Lorraine; Kumar, Vinay; Bennett, Michael
CORPORATE SOURCE: Southwestern Medical Center, University of Texas, Dallas, TX, 75235, USA
SOURCE: Int. Immunol. (1994), 6(9), 1297-306
CODEN: INIMEN; ISSN: 0953-8178
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Murine natural killer (NK) **cells** can mediate specific rejection of **bone marrow cell** (BMC) allografts. Whereas pos. recognition of **allogeneic** MHC antigens forms the basis for T **cell** alloreactivity, it has been postulated that NK **cells** are reactive against targets that do not express certain self-encoded MHC class I antigens.

Here, we study the **immunogenicity** of BMC grafts from two class I **transgenic** mice, D8 (B6 mice with an H-2Dd **transgene**) and C3H.Ld (C3H mice with an H-2Ld **transgene**). D8 BMC grafts are acutely rejected by B6 but not D8 recipients. This suggests that antigenic motifs assocd. with the H-2Dd mol. are recognized. B6 mice depleted of their CD3+ but not NK1.1+ **cells** can still reject D8 BMC grafts. These data suggest that NK1.1+/CD3- **cells** recognize the H-2Dd derived antigenic motifs. Similarly, C3H.Ld BMC grafts are rejected by B6 .times. C3H F1 but not B6 .times. C3H.Ld F1 recipients. Thus, antigenic motifs assocd. with the H-2Ld mol. can also be recognized. Furthermore, expression of either H-2Dd or H-2Ld by the recipients renders them unable to reject D8 or C3H.Ld BMC grafts. Therefore, H-2Dd and H-2Ld mols. appear to express common antigenic motifs recognized by NK **cells**. Addnl. studies with B6.R4 (KbIbSbDr), an intra-H-2 recombinant mouse, indicated that a third class I mol., possibly H-2Dr, also shared the common antigenic motifs with both H-2Dd and H-2Ld mols. Thus, pos. recognition of class I antigens by NK **cells** can occur. However, expression of some of these antigenic motifs appear to be neg. controlled by certain H-2r genes as suggested by rejection of D8 and B6.R4 BMC grafts by D8 .times. B10.RIII F1 and B6.R4 .times. B10.RIII F1 hybrids resp.

L5 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:432938 CAPLUS
DOCUMENT NUMBER: 121:32938
TITLE: Acquisition of **immunogenicity** by AKR leukemic **cells** following DNA-mediated gene transfer is associated with the reduction of constitutive reactive superoxide radicals
AUTHOR(S): Chia, Kwok Y.; Lim, Siew P.; Oei, Audrey A.; Sabapathy, T. Kanaga; Hui, Kam M.
CORPORATE SOURCE: Inst. Mol. Cell Biol., Natl. Univ. Singapore, Singapore, 0511, Singapore
SOURCE: Int. J. Cancer (1994), 57(2), 216-23
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have employed the DNA-mediated gene transfer method to introduce the **allogeneic** major-histocompatibility-complex(MHC)-class I gene H-2Kb into the K36.16 tumor **cells**, H-2k, in order to generate tumor-specific immunity. The acquisition of **immunogenicity** by the H-2Kb-transformed clones following gene transfer is assocd. with the redn. of constitutive reactive superoxide radicals. When the levels of cellular superoxide for the H-2Kb-pos. **immunogenic** clones were detd., they were significantly lower (30 to 60%) than that of the parental K36.16 tumor **cells**. This redn. of superoxide in the H-2Kb-transformed **cells** was assocd. with a significant increase in the level of Cu-Zn superoxide dismutase (SOD) and GPX I, together with a redn. in the DNA-binding form of the NF-.kappa.B transcription factor. The K36.16 parental tumor **cells** were also found to be relatively more resistant to the cytotoxic effects of hydrogen peroxide in vitro. To further support the role of superoxide anion radicals in tumorigenesis, in vivo depletion of glutathione promoted the tumorigenicity of the H-2Kb-transformed clones in (AKR/J .times. C57BL/6/J) F1 mice,

whereas SOD was able to reduce their tumorigenicity. In addn., the presence of R-sulfoxine (BSO) in spleen-**cell** cultures in vitro abolished the ability of the immune lymphocytes to develop into tumor-specific cytotoxic T lymphocytes (CTL). These observations support the concept that oxidative processes in tumor **cells** may have a strong influence on the host response against tumors.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, BIOTECHDS, JAPIO, CANCERLIT' ENTERED AT 12:44:50 ON 17 JAN 2002)

L6 80 S L3
L7 58 S L4

L13 10 S L6 AND CELLULAR

=> s l7 or l13
L14 67 L7 OR L13

PROCESSING COMPLETED FOR L14
L15 35 DUP REM L14 (32 DUPLICATES REMOVED)

L15 ANSWER 1 OF 35 MEDLINE
ACCESSION NUMBER: 2002003226 IN-PROCESS
DOCUMENT NUMBER: 21623290 PubMed ID: 11750037
TITLE: Immunological prevention of spontaneous tumors: a new prospect?.
AUTHOR: Quaglino Elena; Rovero Stefania; Cavallo Federica; Musiani Piero; Amici Augusto; Nicoletti Giordano; Nanni Patrizia; Forni Guido
CORPORATE SOURCE: Department of Clinical and Biological Sciences, Ospedale San Luigi Gonzaga, University of Turin, I-10043, Orbassano, Italy.
SOURCE: IMMUNOLOGY LETTERS, (2002 Feb 1) 80 (2) 75-9. Journal code: GIH; 7910006. ISSN: 0165-2478.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20020102
Last Updated on STN: 20020102

AB Recent demonstrations of the specific immune prevention of mammary cancer in female BALB/c mice **transgenic** for the rat Her-2/neu **oncogene** (BALB-neuT) have resulted in reconsideration of the immune mechanisms that inhibit tumor growth. All the mammary glands of these mice progress asynchronously, but consistently, from hyperplasia to invasive carcinoma. Overexpression of the **oncogene** product p185(neu) is first evident in the rudimentary glands of 3-week-old mice. Carcinogenesis is prevented by vaccination with plasmids coding for the extracellular and transmembrane domains of this p185(neu), or with **allogeneic cells** expressing p185(neu) on their membrane, plus the systemic administration of IL-12. This inhibition is the outcome of a delayed-type hypersensitivity specific for p185(neu) and the production of anti-p185(neu) antibodies that restrain the proliferation of tumor **cells** by stripping p185(neu) from their membrane, whereas cytotoxic T lymphocytes seem devoid of a major role.

L15 ANSWER 2 OF 35 MEDLINE
ACCESSION NUMBER: 2001276244 MEDLINE
DOCUMENT NUMBER: 21259873 PubMed ID: 11359801
TITLE: Overexpression of Bcl-2 differentially restores development of thymus-derived CD4-8+ T **cells** and intestinal intraepithelial T **cells** in IFN-regulatory factor-1-deficient mice.
AUTHOR: Ohteki T; Maki C; Koyasu S
CORPORATE SOURCE: Department of Microbiology and Immunology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.
SOURCE: JOURNAL OF IMMUNOLOGY, (2001 Jun 1) 166 (11) 6509-13. Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20010820
Entered Medline: 20010816

AB Mice lacking IFN-regulatory factor (IRF)-1 have reduced numbers of mature CD8+ T **cells** within the thymus and peripheral lymphoid organs, suggesting a critical role of IRF-1 in CD8(+) T **cell** differentiation. Here we show that endogenous Bcl-2 expression is substantially reduced in IRF-1(-/-)CD8+ thymocytes and that introduction of a human Bcl-2 **transgene** driven by Emu or lck promoter in IRF-1(-/-) mice restores the CD8(+) T **cell** development. Restored CD8+ T **cells** are functionally mature in terms of **allogeneic** MLR and cytokine production. In contrast to thymus-derived CD8+ T **cells**, other lymphocyte subsets including NK, NK T, and TCR-gammadelta(+) intestinal intraepithelial lymphocytes, which are also impaired in IRF-1(-/-) mice, are not rescued by expressing human Bcl-2. Our results indicate that IRF-1 differentially regulates the development of these lymphocyte subsets and that survival signals involving Bcl-2 are critical for the development of thymus-dependent CD8+ T **cells**.

L15 ANSWER 3 OF 35 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001213253 MEDLINE
DOCUMENT NUMBER: 21103259 PubMed ID: 11160287
TITLE: Peripheral deletion after **bone marrow** transplantation with costimulatory blockade has features of both activation-induced **cell** death and passive **cell** death.
AUTHOR: Wekerle T; Kurtz J; Sayegh M; Ito H; Wells A; Bensinger S; Shaffer J; Turka L; Sykes M
CORPORATE SOURCE: BMT Section, Transplantation Biology Research Center, Massachusetts General Hospital/Harvard Medical School, Boston, MA 02129, USA.
CONTRACT NUMBER: R01 HL49915 (NHLBI)
SOURCE: JOURNAL OF IMMUNOLOGY, (2001 Feb 15) 166 (4) 2311-6. Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20010425
Entered Medline: 20010419

AB Two major pathways of death of previously activated T **cells** have been described: activation-induced **cell** death can be triggered by restimulating activated T **cells** with high concentrations of Ag, is Fas-dependent, is not influenced by proteins of the Bcl family, and is blocked by cyclosporin A; in contrast, passive **cell** death is induced by the withdrawal of growth factors and activation stimuli, is Fas-independent, and is blocked by Bcl family proteins. We examined the role of these two forms of **cell** death in the peripheral deletion of donor-reactive host T **cells** after **allogeneic** **bone marrow** transplantation and costimulatory blockade with anti-CD154 plus CTLA4Ig in two murine models. The substantial decline in donor-reactive CD4 **cells** seen in wild-type recipients 1 wk after **bone marrow** transplantation with costimulatory blockade was largely inhibited in Fas-deficient recipients and in Bcl-x(L)-**transgenic** recipients. We observed these effects both in a model involving low-dose total body irradiation and a conventional dose of **bone marrow**, and in a radiation-free regimen using high-dose **bone marrow** transplantation. Furthermore, cyclosporin A did not completely block the deletion of donor-reactive CD4(+) T **cells** in recipients of **bone marrow** transplantation with costimulatory blockade. Thus, the deletion of donor-reactive T **cells** occurring early after **bone marrow** transplantation with costimulatory blockade has features of both activation-induced **cell** death and passive **cell** death. Furthermore, these in vivo data demonstrate for the first time the significance of in vitro results indicating that proteins of the Bcl family can prevent Fas-mediated apoptosis under certain circumstances.

L15 ANSWER 4 OF 35 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001668107 IN-PROCESS
DOCUMENT NUMBER: 21553253 PubMed ID: 11696586
TITLE: Combined **allogeneic** tumor **cell** vaccination and systemic interleukin 12 prevents mammary carcinogenesis in HER-2/neu **transgenic** mice.
AUTHOR: Nanni P; Nicoletti G; De Giovanni C; Landuzzi L; Di Carlo E; Cavallo F; Pupa S M; Rossi I; Colombo M P; Ricci C; Astolfi A; Musiani P; Forni G; Lollini P L
CORPORATE SOURCE: Cancer Research Section, Department of Experimental Pathology, University of Bologna, Italy.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (2001 Nov 5) 194 (9) 1195-205.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20011121
Last Updated on STN: 20011121

AB **Transgenic** Balb/c mice expressing the transforming rat

HER-2/neu **oncogene** develop early and multifocal mammary carcinomas. Within the first 5 months of life the tissue-specific expression of HER-2/neu causes a progression in all their 10 mammary glands from atypical hyperplasia to invasive carcinoma. It was previously observed that chronic administration of interleukin (IL)-12 increased tumor latency, but every mouse eventually succumbed to multiple carcinomas. A significant improvement in tumor prevention was sought by administering **allogeneic** mammary carcinoma **cells** expressing HER-2/neu combined with systemic IL-12. This treatment reduced tumor incidence by 90% and more than doubled mouse lifetime. For the maximum prevention p185(neu) antigen must be expressed by **allogeneic** **cells**. IL-12 treatment strongly increased the **cell** vaccine efficacy. The mammary glands of mice receiving the combined treatment displayed a markedly reduced epithelial **cell** proliferation, angiogenesis, and HER-2/neu expression, while the few hyperplastic foci were heavily infiltrated by granulocytes, macrophages, and CD8(+) lymphocytes. Specific anti-HER-2/neu antibodies were produced and a nonpolarized activation of CD4(+) and CD8(+) **cells** secreting IL-4 and interferon (IFN)-gamma were evident. A central role for IFN-gamma in the preventive effect was proven by the lack of efficacy of vaccination in IFN-gamma gene knockout HER-2/neu **transgenic** Balb/c mice. A possible requirement for IFN-gamma is related to its effect on antibody production, in particular on IgG2a and IgG2b subclasses, that were not induced in IFN-gamma knockout HER-2/neu mice. In conclusion, our data show that an **allogeneic** HER-2/neu-expressing **cell** vaccine combined with IL-12 systemic treatment can prevent the onset of genetically determined tumors.

L15 ANSWER 5 OF 35 MEDLINE
ACCESSION NUMBER: 2001530655 MEDLINE
DOCUMENT NUMBER: 21461160 PubMed ID: 11577350
TITLE: Circumventing tolerance to a human **MDM2** -derived tumor antigen by TCR gene transfer.
COMMENT: Comment in: Nat Immunol. 2001 Oct;2(10):900-1
AUTHOR: Stanislawski T; Voss R H; Lotz C; Sadovnikova E; Willemsen R A; Kuball J; Ruppert T; Bolhuis R L; Melief C J; Huber C; Stauss H J; Theobald M
CORPORATE SOURCE: Department of Hematology and Oncology, Johannes Gutenberg University, D-55101 Mainz, Germany.
SOURCE: Nat Immunol, (2001 Oct) 2 (10) 962-70. Journal code: D0G; 100941354. ISSN: 1529-2908.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200111
ENTRY DATE: Entered STN: 20011001
Last Updated on STN: 20011105
Entered Medline: 20011101

AB We identified a tumor-associated cytotoxic T lymphocyte (CTL) epitope derived from the widely expressed human **MDM2** oncoprotein and were able to bypass self-tolerance to this tumor antigen in HLA-A*0201 (A2.1) **transgenic** mice and by generating A2.1-negative, allo-A2.1-restricted human T lymphocytes. A broad range of malignant, as opposed to nontransformed **cells**, were killed by high-avidity **transgenic**

mouse and **allogeneic** human CTLs specific for the A2.1-presented **MDM2** epitope. Whereas the self-A2.1-restricted human T **cell** repertoire gave rise only to low-avidity CTLs unable to recognize the natural **MDM2** peptide, human A2.1+ T lymphocytes were turned into efficient **MDM2**-specific CTLs upon expression of wild-type and partially humanized high-affinity T **cell** antigen receptor (TCR) genes derived from the **transgenic** mice. These results demonstrate that TCR gene transfer can be used to circumvent self-tolerance of autologous T lymphocytes to universal tumor antigens and thus provide the basis for a TCR gene transfer-based broad-spectrum immunotherapy of malignant disease.

L15 ANSWER 6 OF 35 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001140774 EMBASE
TITLE: UVB-irradiated dendritic **cells** are impaired in their **APC** function and tolerize primed Th1 **cells** but not naive CD4+ T **cells**.
AUTHOR: Denfeld R.W.; Hara H.; Tesmann J.P.; Martin S.; Simon J.C.
CORPORATE SOURCE: Dr. R.W. Denfeld, Department of Dermatology, Albert-Ludwigs-Universitat, Hauptstrasse 7, 79104 Freiburg, Germany. denfeld@haut.ukl.uni-freiburg.de
SOURCE: Journal of Leukocyte Biology, (2001) 69/4 (548-554). Refs: 24
ISSN: 0741-5400 CODEN: JLBIE7
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 014 Radiology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have shown that low-dose UVB radiation converts Langerhans **cells** (LC) from **immunogenic** to tolerogenic **APC**. Therefore, we questioned whether low-dose UVB irradiation of **bone marrow**-derived dendritic **cells** (DC) alters their **APC** function, thereby inducing tolerance in T **cells**. To address this issue, cocultures of DC; and naive, **allogeneic** T **cells**; naive, OVA-specific TCR-**transgenic** T **cells** from DO11.10 mice; or primed, antigen-specific T **cells** using the Th1 clone AE7 were analyzed. First, we found low-dose UVB-irradiated DC (UVB-DC) to dose-dependently (50-200 J/m(2)) inhibit T-**cell** proliferation of naive and primed T **cells**. In addition, supernatants harvested from cocultures of UVB-DC and naive T **cells** showed markedly reduced levels of IL-2 and IFN-.gamma. and to a lesser degree of IL-4 and IL-10, suggesting a preferential down-regulation of Th1 responses by UVB-DC. FACS analysis of UVB-DC revealed no changes in surface expression of MHC, costimulatory, and adhesion molecules. To test tolerance induction, allo- or antigen-specific T **cells** isolated from cocultures with unirradiated DC and UVB-DC were restimulated with unirradiated DC or IL-2. It is interesting that UVB-DC induced antigen-specific tolerance in the Th1 clone AE7. In contrast, UVB-DC induced a partial inhibition of **allogeneic** T-**cell** proliferation but no tolerance with similar unresponsiveness to restimulation with IL-2 and unirradiated DC

irrespective of their haplotype. Similar observations were made when naive, TCR-**transgenic** T **cells** from DO11.10 mice were used. In conclusion, UVB-DC are impaired in their **APC** function and tolerize the primed antigen-specific Th1 clone AE7 but not naive allo- or OVA-specific T **cells**.

L15 ANSWER 7 OF 35 MEDLINE
ACCESSION NUMBER: 2001166340 MEDLINE
DOCUMENT NUMBER: 21165161 PubMed ID: 11264705
TITLE: Effect of localized cytokine dysregulation: accelerated rejection of IL-2-expressing skin grafts.
AUTHOR: Blackburn C; Grogan J L; Augustine C L; Miller J F; Varigos G; Morahan G
CORPORATE SOURCE: Walter and Eliza Hall Institute of Medical Research and Royal Melbourne Hospital, PO Royal Melbourne Hospital, Victoria, Australia.
SOURCE: IMMUNOLOGY AND CELL BIOLOGY, (2001 Apr) 79 (2) 128-31.
Journal code: GH8; 8706300. ISSN: 0818-9641.
PUB. COUNTRY: Australia
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB **Transgenic** mice were created in which a sheep keratin promoter directed the expression of IL-2 into the dermis. These KIL-2 **transgenic** mice were used to investigate the effects of localized IL-2 dysregulation on immune responses. Peripheral tolerance to skin antigens was not broken by in situ IL-2 expression because syngeneic KIL-2 skin grafts were not rejected. However, MHC Class I-disparate skin grafts from KIL-2 donors were rejected faster (median survival time (MST) 12 days) than grafts of non-**transgenic** littermate skin (MST 18 days). In contrast, the kinetics of KIL-2 H-Y-disparate skin graft rejection (MST 14 days) did not differ significantly from controls (MST 16 days), suggesting that upregulation of IL-2 at the effector site could affect CD4+ T **cell**- independent, but not CD4+ T **cell**-dependent, responses. No effect on rejection kinetics was observed when wild type **allogeneic** skin was grafted onto **transgenic** mice that expressed bcl2 constitutively in their lymphocytes (MST of 14 days, both sets), indicating that this was not simply due to increased longevity of T **cells** within the IL-2 expressing graft. We therefore suggest that aberrant expression of IL-2 can accelerate helper-independent CD8+ T **cell** responses by increasing proliferation and/or differentiation of cytolytic T **cells** at the effector site.

L15 ANSWER 8 OF 35 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-182543 [16] WPIDS
DOC. NO. NON-CPI: N2000-134646
DOC. NO. CPI: C2000-057155
TITLE: **Cellular immunogens** comprising **allogenic** donor **cells** transfected with a construct comprising a proto-**oncogene** cognate, useful as cancer

vaccines.
DERWENT CLASS: B04 D16 P33
INVENTOR(S): ENGLAND, J M; HALPERN, M S
PATENT ASSIGNEE(S): (ENGL-I) ENGLAND J M; (HALP-I) HALPERN M S;
(UYAL-N) UNIV ALLEGHNEY HEALTH SCI
COUNTRY COUNT: 87
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000004927	A1	20000203	(200016)*	EN	77

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

AU 9949819	A	20000214	(200029)	
EP 1100544	A1	20010523	(200130)	EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000004927	A1	WO 1999-US15594	19990708
AU 9949819	A	AU 1999-49819	19990708
EP 1100544	A1	EP 1999-933855	19990708
		WO 1999-US15594	19990708

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9949819	A	Based on	WO 200004927
EP 1100544	A1	Based on	WO 200004927

PRIORITY APPLN. INFO: US 1998-93965P 19980724
AN 2000-182543 [16] WPIDS
AB WO 200004927 A UPAB: 20000330
NOVELTY - A **cellular immunogen** (I) comprising **allogenic cells** transfected with **transgene** construct (II) comprising a **transgene** cognate to target proto-**oncogene** and a strong promoter, is new.
DETAILED DESCRIPTION - A **cellular immunogen** comprising **allogenic** donor **cells** transfected with **transgene** construct (II), is useful for immunizing a host against the products of a target proto-**oncogene**. The gene product of (II) induces host immunoreactivity of host self determinants of the product of the target proto-**oncogene**.
An INDEPENDENT CLAIM is also included for a method of preparing (I) comprising transfecting **allogenic** donor **cells** with (II).
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - Vaccine; gene therapy.
USE - (I) is useful for vaccinating a host against cancer by inserting (I) into the body of the host for the expression of (II)

(claimed).

ADVANTAGE - Unlike prior vaccination methods designed to target such mutation-driven non-self determinants, (I) induce reactivity for self-determinants in the over expressed product of tumor associated and over expressed proto-**oncogenes**.

Dwg.0/3

L15 ANSWER 9 OF 35 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000511777 MEDLINE
DOCUMENT NUMBER: 20518814 PubMed ID: 11069032
TITLE: De novo acute B **cell** leukemia/lymphoma with t(14;18).
AUTHOR: Stamatoullas A; Buchonnet G; Lepretre S; Lenain P; Lenormand B; Duval C; Callat M P; Gaulard P; Bastard C; Tilly H
CORPORATE SOURCE: Departement d'Hematologie, Centre Henri Becquerel, Rouen, France.
SOURCE: LEUKEMIA, (2000 Nov) 14 (11) 1960-6.
Journal code: LEU. ISSN: 0887-6924.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001122

AB The t(14;18)(q32;q21) translocation is the most common translocation in B **cell** malignancies being found in 80% of follicular lymphomas and about 20% of diffuse large B **cell** lymphomas. Only rare cases of de novo acute B **cell** lymphoblastic leukemia with t(14;18) have been described. We describe five cases of this entity which appears to have very homogeneous clinical, phenotypic and genotypic features. None of these patients had prior history of follicular lymphoma. The disease was characterized by acute clinical features with nodal and/or extranodal disease, massive **bone marrow** infiltration and rapid increase of circulating blast **cells** of mature B **cell** phenotype. All patients disclosed complex chromosomal and molecular abnormalities involving at least the BCL-2 and **c-MYC** genes. Furthermore, three patients had evidence of BCL-6 involvement and one patient had a p53 mutation. Despite intensive chemotherapy, including for two patients **allogeneic bone marrow** transplantation in first complete remission, all patients died within a few months. Neuro-meningeal relapse occurred in three of the five patients in spite of neuro-meningeal prophylaxis. De novo leukemia/lymphoma with t(14;18) is a rare entity with a very poor prognosis. Whether early **bone marrow** transplant could modify the natural history of the disease remains to be determined. An intensive neuro-meningeal prophylaxis appears to be mandatory in these patients.

L15 ANSWER 10 OF 35 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000395303 MEDLINE
DOCUMENT NUMBER: 20341163 PubMed ID: 10880747
TITLE: Granulocyte colony-stimulating factor perturbs lymphocyte mitochondrial function and inhibits

cell cycle progression.

AUTHOR: Rutella S; Rumi C; Pierelli L; Morosetti R; Sica S; Bonanno G; Scambia G; Leone G
CORPORATE SOURCE: Department of Hematology, Catholic University, Rome, Italy.. sergiorutella@tin.it

SOURCE: EXPERIMENTAL HEMATOLOGY, (2000 Jun) 28 (6) 612-25. Journal code: EPR; 0402313. ISSN: 0301-472X.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000824
Last Updated on STN: 20000824
Entered Medline: 20000817

AB Sera from healthy subjects receiving recombinant human granulocyte colony-stimulating factor (rHuG-CSF) to mobilize CD34(+) peripheral blood progenitors (PBPC) have been recently shown to induce unresponsiveness of **allogeneic** lymphocytes to mitogenic challenge. In the present investigation, the effects of rHuG-CSF on the early stages of lymphocyte activation-induced apoptosis and on lymphocyte **cell** cycle entry were evaluated.Sera were obtained from HLA-identical donors receiving rHuG-CSF to mobilize CD34(+) PBPC for **allogeneic** transplantation. Normal peripheral blood mononuclear **cells** (PBMC) were challenged with phytohemagglutinin (PHA) in the presence of serum collected before (preG) or after rHuG-CSF administration (postG). Mitochondrial function, that is, incorporation of 3,3'-dihexyloxacarbocyanine iodide [DiOC(6)(3)] and generation of reactive oxygen species (ROS) as well as expression of **c-Myc** and Bcl-2 family members (Bcl-2, Bcl-X(L), Bax) were evaluated by multiparameter flow cytometry. The activation-induced fragmentation of genomic DNA was detected by highly sensitive LM-PCR assay.CD4(+)DiOC(6)(3)(low) and CD8(+)DiOC(6)(3)(low) T lymphocytes increased and reached 32% (range 27%-38%) and 20% (range 15%-23%) of circulating T **cells**, respectively, on day 4 of rHuG-CSF administration. Hypergeneration of ROS could be demonstrated in 65% (range 58%-82%) of CD4(+) T lymphocytes and in 0.4% (range 0.2%-0.8%) of circulating CD8(+) T **cells**. rHuG-CSF determined no alteration of mitochondrial function if added to **allogeneic** PBMC in vitro, thus suggesting indirect effects mediated by soluble factors; on the contrary, when PBMC were challenged with PHA in the presence of postG serum, both perturbation of mitochondrial transmembrane potential (Deltapsi(m)) and hypergeneration of ROS were induced, and lymphocytes were predominantly arrested in a G(0)-like phase of the **cell** cycle and displayed genomic DNA fragmentation. Interestingly, the preincubation of PBMC with a blocking antibody directed against CD95 abrogated the perturbation of lymphocyte Deltapsi(m), suggesting that the CD95 signaling pathway might play a role in the induction of apoptosis after PHA stimulation in the presence of postG serum. Moreover, Bax protein was overexpressed in postG (median fluorescence intensity = 180, range 168-186) compared with preG cultures (median fluorescence intensity = 75, range 68-80; $p < 0.01$), while no differences in Bcl-2, Bcl-X(L), and **c-Myc** staining intensity were observed.Our findings demonstrate a humoral-mediated rHuG-CSF-induced dissipation of lymphocyte mitochondrial Deltapsi(m); these effects might be mediated by Bax overexpression,

with imbalance between apoptosis-promoting and apoptosis-inhibiting Bcl-2 family members and with subsequent induction of mitochondrial permeability transition. Whether immune dysfunction will favorably impact on incidence and severity of acute graft vs host disease after **allogeneic** PBPC transplantation remains to be determined.

L15 ANSWER 11 OF 35 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000134076 EMBASE
TITLE: Unusual patterns of alloimmunity evoked by **allogeneic** liver parenchymal **cells**.
AUTHOR: Bumgardner G.L.; Orosz C.G.
CORPORATE SOURCE: G.L. Bumgardner, The Ohio State University, 1654 Upham Drive, 373 Means Hall, Columbus, OH 43210-1250, United States. bumgardner-1@medctr.osu.edu
SOURCE: Immunological Reviews, (2000) 174/- (260-279).
Refs: 156
ISSN: 0105-2896 CODEN: IMRED2
COUNTRY: Denmark
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 009 Surgery
026 Immunology, Serology and Transplantation
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Despite the widely accepted view of the liver as an immunoprivileged tissue, purified **allogeneic** liver parenchymal **cells** delivered to the liver of a recipient mouse are highly antigenic. A functional **transgenic** model of hepatocyte transplantation in mice is used to explore host immune responses to **allogeneic** hepatocytes. Transplanted hepatocytes expressing human alpha-1-antitrypsin (hA1AT) are monitored for survival by the secretion of the **transgene** product hA1AT. Transplantation of **transgenic** hepatocytes into syngeneic or immunoincompetent severe combined immunodeficiency disease (SCID) mice results in indefinite hepato-**cellular** allograft survival. However, transplantation of **transgenic** hepatocytes into **allogeneic** hosts results in rapid hepatocyte rejection. This rejection response is associated with prominent delayed type hypersensitivity responses to **cellular** alloantigen but minimal donor-reactive humoral immunity. Hepatocyte rejection is not controlled by host treatment with anti-CD4 mAb despite the ability of the same treatment regimen to produce indefinite survival of donor-matched heart allografts. Host immune responses to **allogeneic** hepatocytes utilize CD40L/CD40 but not CD28/B7 co-stimulation, unlike the activation of both of these systems in responses to other allografts. Furthermore, C57BL/6 mice which have been induced by anti-CD4 mAb or gallium nitrate treatment to accept heart allografts promptly reject donor-matched **transgenic** hepatocytes. Studies in reconstituted SCID, CD4 knockout (KO), and CD8 KO mice demonstrate that hepatocyte rejection can be initiated independently by either CD4+ T **cells** or CD8+ T **cells**, which again diverges from what has been observed for most other types of allografts. This may account for the relative resistance to immunoprotection for hepatocellular allografts with conventional immunosuppressive agents and to immunoregulatory states induced by other allografts. Three models of hepatocyte rejection are

discussed.

L15 ANSWER 12 OF 35 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999345234 MEDLINE
DOCUMENT NUMBER: 99345234 PubMed ID: 10418893
TITLE: Xenogeneic and **allogeneic** anti-MHC immune responses induced by plasmid DNA immunization.
AUTHOR: Dela Cruz C S; Chamberlain J W; MacDonald K S; Barber B H
CORPORATE SOURCE: Institute of Medical Sciences, University of Toronto, Ontario, Canada.
SOURCE: VACCINE, (1999 Jun 4) 17 (20-21) 2479-92.
Journal code: X60; 8406899. ISSN: 0264-410X.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990910
Last Updated on STN: 19990910
Entered Medline: 19990826

AB Major histocompatibility complex (MHC) proteins are known to be incorporated into the human immunodeficiency virus (HIV-1) envelope as the virion buds from the host **cell** surface. Studies using simian immunodeficiency virus (SIV) infection of macaques have demonstrated that immunization with uninfected human **cells** or purified HLA proteins can provide protection from challenge with live SIV when it is grown in human **cells** expressing the same MHC alleles. Thus the induction of anti-MHC immune responses represents an important option to consider with respect to vaccine design for SIV and HIV. Here we examine plasmid DNA immunization strategies as an alternative to **cellular** or protein **immunogens** for the induction of xenogeneic and **allogeneic** immune responses in C57BL/6 mice and in an HLA **transgenic** mouse model system, respectively. We compared the **immunogenicity** of HLA-A2- and HLA-B27-expressing splenocytes with the corresponding plasmid DNA **immunogens**. Results from the **transgenic** mouse experiments indicate that plasmid DNA immunization with both class I and class II MHC-encoding vectors can elicit antibody responses recognizing conformationally intact MHC molecules. Our data also show that immunization with class I MHC-encoding DNA **immunogens** can elicit cytotoxic T-lymphocyte responses, demonstrating the potential to mobilize both antibody and **cell**-mediated anti-MHC immune responses in the context of this approach to HIV-1 vaccine design.

L15 ANSWER 13 OF 35 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 6
ACCESSION NUMBER: 1999338513 EMBASE
TITLE: Targeting HER-2/neu for active-specific immunotherapy in a mouse model of spontaneous breast cancer.
AUTHOR: Cefai D.; Morrison B.W.; Sckell A.; Favre L.; Balli M.; Leunig M.; Gimmi C.D.
CORPORATE SOURCE: C.D. Gimmi, Department of Clinical Research, University of Bern, Murtenstrasse 35, 3010 Bern, Switzerland. gimmi@dkf5.unibe.ch
SOURCE: International Journal of Cancer, (1999) 83/3 (393-400).

Refs: 23
ISSN: 0020-7136 CODEN: IJCNAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The identification of tumor-associated antigens has led to increased interest in vaccination strategies to treat and/or prevent cancer. This study examined the feasibility of active-specific immunotherapy against the breast- tumor antigen HER-2/neu using a HER-2/neu **transgenic** (rNeu-TG) mouse model, rNeu-TG mice develop spontaneous breast tumors after pregnancy, indicating that they fail to mount an effective immune response against rNeu. **Allogeneic fibroblasts** expressing HER-2/neu were used as a **cell**-based vaccine. Vaccination induced a rNeu-specific anti-tumor immune response that prevented tumor formation of transplanted breast-tumor **cells**, and also protected mice from spontaneous tumor formation. Both T-**cell** -mediated and humoral immune responses were detectable in vaccinated mice. Vaccination also protected tumor-bearing mice from a challenge with **cell** suspensions isolated from spontaneous tumors, indicating that rNeu-TG mice are not tolerant to rNeu, even after spontaneous tumor formation. However, established spontaneous tumors themselves were never affected. This observation correlated with T-**cell** infiltrations in the injected but not in the established spontaneous tumor. Thus, **allogeneic fibroblasts** are efficient vaccine vectors to prime a specific immune response against an over-expressed tumor antigen. Moreover, our results suggest striking differences in the immunological requirements for the rejection of an established w a transplanted tumor.

L15 ANSWER 14 OF 35 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1999:669540 SCISEARCH
THE GENUINE ARTICLE: BN31W
TITLE: Genetically engineered pancreatic beta-**cell** lines for **cell** therapy of diabetes
AUTHOR: Efrat S (Reprint)
CORPORATE SOURCE: ALBERT EINSTEIN COLL MED, DEPT MOL PHARMACOL, 1300 MORRIS PK AVE, BRONX, NY 10461 (Reprint); TEL AVIV UNIV, SACKLER SCH MED, DEPT HUMAN GENET & MOL MED, IL-69978 TEL AVIV, ISRAEL
COUNTRY OF AUTHOR: USA; ISRAEL
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (AUG 1999) Vol. 875, pp. 286-293.
Publisher: NEW YORK ACAD SCIENCES, 2 EAST 63RD ST, NEW YORK, NY 10021.
ISSN: 0077-8923.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 22

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The optimal treatment of Insulin-dependent diabetes mellitus (IDDM), which is caused by the autoimmune destruction of pancreatic: islet beta **cells**, would require the regulated delivery of

insulin by transplantation of functional beta **cells**. beta-**cell** transplantation has so far been restricted by the scarcity of human islet donors. This shortage would be alleviated by the development of differentiated p-**cell** lines, which could provide an abundant and well-characterized source of beta tells for transplantation. Using conditional transformation approaches, our laboratory has generated continuous beta-**cell** lines from **transgenic** mice. These **cells** produce insulin amounts comparable to those of normal islets and release insulin in response to physiological stimuli. **Cell** replication in these beta **cells** can be tightly controlled both in culture and in vivo, allowing regulation of **cell** number and **cell** differentiation. Another challenge to **cell** therapy of IDDM is the protection of transplanted **cells** from immunological rejection and recurring autoimmunity. By employing adenovirus genes which downregulate **antigen presentation** and increase **cell** resistance to cytokines, beta-**cell** transplantation across **allogeneic** barriers was achieved without immunosuppression, In principle, similar beta-**cell** lines can be derived from isolated human islets using viral vectors to deliver conditionally regulated transforming and immunomodulatory genes into beta **cells**. The combination of these approaches with immunoisolation devices holds the promise of a widely available **cell** therapy for treatment of IDDM in the near future.

L15 ANSWER 15 OF 35 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999303899 EMBASE
TITLE: Current results with myeloablative therapy with hematopoietic support in advanced neuroblastoma.
AUTHOR: Matthay K.K.
CORPORATE SOURCE: Prof. K.K. Matthay, Pediatric Clinical Oncology, University California San Francisco, 505 Parnassus, San Francisco, CA 94143-0106, United States. katekm@itsa.ucsf.edu
SOURCE: Cancer Research Therapy and Control, (1999) 9/1-2 (89-94).
Refs: 29
ISSN: 1064-0525 CODEN: CRTCEA
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Neuroblastoma is the third most common malignancy in childhood and accounts for at least 15% of cancer related deaths in children. Sixty percent of children with neuroblastoma have disseminated disease at diagnosis. Biologic risk factors like MYCN amplifications and unfavorable Shimada histopathologic classification also indicate high risk disease. Despite the use of increasingly aggressive combined modality treatments, which have increased the remission rate and duration, the long-term survival for Stage IV disease in previous decades has been less than 15%. The addition of increased dose intensity and myeloablative therapy has resulted in an improvement in survival in the current decade. Recent retrospective

comparisons of chemotherapy alone to high dose chemoradiotherapy followed by **allogeneic** or autologous purged **bone marrow** transplantation suggest a possible advantage for myeloablative therapy, particularly in the highest risk patients, although this must be validated in the current CCG prospective randomized trial. Other unanswered questions include the role of tumor contamination of stem **cells** and the use of total body irradiation. Future progress may also be made by the addition of tumor specific biologic agents to the therapeutic armamentarium, including differentiating agents, immunologic agents, or targeted radiotherapy.

L15 ANSWER 16 OF 35 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1999094434 MEDLINE
DOCUMENT NUMBER: 99094434 PubMed ID: 9879825
TITLE: Chronic myelogenous leukemia: molecular and cellular aspects.
AUTHOR: Pasternak G; Hochhaus A; Schultheis B; Hehlmann R
CORPORATE SOURCE: III. Medizinische Klinik, Klinikum Mannheim der Universitat Heidelberg, Mannheim, Germany.
SOURCE: JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, (1998) 124 (12) 643-60. Ref: 148
Journal code: HL5; 7902060. ISSN: 0171-5216.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990128
Last Updated on STN: 19990128
Entered Medline: 19990112

AB Chronic myelogenous leukemia (CML) originates in a pluripotent hematopoietic stem **cell** of the **bone marrow** and is characterized by greatly increased numbers of granulocytes in the blood. Myeloid and other hematopoietic **cell** lineages are involved in the process of clonal proliferation and differentiation. After a period of 4-6 years the disease progresses to acute-stage leukemia. On the cellular level, CML is associated with a specific chromosome abnormality, the t(9; 22) reciprocal translocation that forms the Philadelphia (Ph) chromosome. The Ph chromosome is the result of a molecular rearrangement between the c-ABL proto-**oncogene** on chromosome 9 and the BCR (breakpoint cluster region) gene on chromosome 22. Most of ABL is linked with a truncated BCR. The BCR/ABL fusion gene codes for an 8-kb mRNA and a novel 210-kDa protein which has higher and aberrant tyrosine kinase activity than the normal c-ABL-coded counterpart. Phosphorylation of a number of substrates such as GAP, GRB-2, SHC, FES, CRKL, and paxillin is considered a decisive step in transformation. An etiological connection between BCR/ABL and leukemia is indicated by the observation that **transgenic** mice bearing a BCR/ABL DNA construct develop leukemia of B, T, and myeloid **cell** origin. CML **cells** proliferate and expand in an almost unlimited manner. Adhesion defects in **bone marrow** stromal **cells** have been proposed to explain the increased number of leukemic **cells** in the peripheral blood. However,

findings of our laboratory have shown that the BCR/ABL chimeric protein that is expressed in transfected **cells** may, under certain conditions, also increase the adhesion to fibronectin via enhanced expression of integrin. Our previous immunocytological studies on the expression of beta1 and beta2 integrins have found no qualitative differences between normal and CML hematopoietic **cells** in vitro. Even long-term-cultured CML **bone marrow** or blood **cells** continuously express those adhesion molecules that are characteristic of the cytological type. Recent experiments indicate that certain early CML progenitors may adhere to the stromal layer in vitro similarly to their normal counterparts. They cannot be completely removed by long-term culture on **allogeneic** stromal **cells**. At present, the only curative therapy is transplantation of **allogeneic** hematopoietic stem **cells**. Based on the molecular and cellular state of knowledge of CML, new therapies are being developed. BCR/ABL antisense oligonucleotides, inhibitors of tyrosine kinase, peptide-specific adoptive immunotherapy or peptide vaccination, and restoration of hematopoiesis by autologous stem **cell** transplantation following CML **cell** purging are examples of important approaches to improving CML treatment.

L15 ANSWER 17 OF 35 JICST-EPlus COPYRIGHT 2002 JST
ACCESSION NUMBER: 980389488 JICST-EPlus
TITLE: Multiple myeloma: new aspects of biology and treatment.
AUTHOR: OZAKI S; KOSAKA M
CORPORATE SOURCE: Univ. Tokushima School of Medicine, Tokushima, JPN
SOURCE: J Med Invest, (1998) vol. 44, no. 3/4, pp. 127-136. Journal Code: G0657A (Fig. 2, Tbl. 2, Ref. 98) ISSN: 1343-1420
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
STATUS: New
AB Recently, considerable progress has been made in understanding of the biology and treatment of multiple myeloma. Molecular genetic abnormalities such as bcl-2,**c-myc**, ras, p53, and Rb genes have been identified in this disease and are related to a poor prognosis. Cytokine studies have revealed that interleukin-6 is a potent growth factor for myeloma **cells** and is also responsible for the progressive bone resorption together with interleukin-1 .BETA. and tumor necrosis factor. Myeloablative chemotherapy followed by **allogeneic** or autologous hematopoietic stem **cell** transplantation has increased the incidence of complete remission. However, relapses are still observed because of drug resistance of tumor **cells**. Immunotherapeutic approaches targeting to **cell** surface antigens and interleukin-6 signals are being developed to further eliminate myeloma **cells**. Translating new biological advances into treatment protocols is essential to improve the prognosis of multiple myeloma. (author abst.)

L15 ANSWER 18 OF 35 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1998107832 MEDLINE
DOCUMENT NUMBER: 98107832 PubMed ID: 9448143
TITLE: In vivo **immunogenicity** of purified **allogeneic** hepatocytes in a murine hepatocyte

transplant model.

AUTHOR: Bumgardner G L; Li J; Heininger M; Ferguson R M; Orosz C G
CORPORATE SOURCE: Department of Surgery, Ohio State University, Columbus 43210, USA.
SOURCE: TRANSPLANTATION, (1998 Jan 15) 65 (1) 47-52.
Journal code: WEJ; 0132144. ISSN: 0041-1337.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980224
Last Updated on STN: 19980224
Entered Medline: 19980211

AB BACKGROUND. It has been reported previously that liver grafts and liver **cells** seem to be tolerogenic, based on the high frequency of spontaneous tolerance after orthotopic liver transplantation in rodents and on the phenomenon of portal venous tolerance in other models. The purpose of the current study was to characterize in vivo immune responses to **allogeneic** hepatocytes transplanted into the portal circulation. METHODS. In this functional model of hepatocyte transplantation, "donor" hepatocytes from mice **transgenic** for human alpha1-antitrypsin (hA1AT) were transplanted by intrasplenic injection into host mice and the secreted hA1AT protein measured in host serum to determine hepatocellular graft survival. Host immune responses were assessed by measurement of donor-specific alloantibodies and delayed-type hypersensitivity responses. In some experiments, liver nonparenchymal **cells** (NPCs) were co-transplanted with the **allogeneic** hepatocyte transplant. RESULTS. **Allogeneic** hepatocyte transplant into immunocompetent hosts resulted in loss of host serum hA1AT by days 7-10 after transplant, whereas syngeneic hosts maintained long-term hepatocellular graft survival as reflected by persistence of serum hA1AT for > 20 weeks. **Allogeneic** hepatocyte transplantation resulted in the development of donor-specific alloantibody and delayed-type hypersensitivity responses, as well as a "second set" response of accelerated hepatocellular graft rejection after a second transplant. Pretransplantation or co-transplantation of donor-matched liver NPCs at the time of **allogeneic** hepatocyte transplantation did not prolong hepatocellular allograft survival. CONCLUSIONS. **Allogeneic** hepatocytes introduced into the portal circulation via intrasplenic injection are **immunogenic** not tolerogenic and stimulate a weak humoral and strong **cell** mediated host immune response in vivo. Co-transplantation or pretransplantation of **allogeneic** liver NPCs did not protect **allogeneic** hepatocytes from immunologic rejection.

L15 ANSWER 19 OF 35 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1998:162891 SCISEARCH
THE GENUINE ARTICLE: YX518
TITLE: Molecular genetics of childhood leukemias
AUTHOR: Rubnitz J E (Reprint); Look A T
CORPORATE SOURCE: ST JUDE CHILDRENS HOSP, DEPT HEMATOL ONCOL, 332 N LAUDERDALE ST, MEMPHIS, TN 38105 (Reprint); ST JUDE CHILDRENS HOSP, DEPT EXPT ONCOL, MEMPHIS, TN 38105;

UNIV TENNESSEE, COLL MED, DEPT PEDIAT, MEMPHIS, TN
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF PEDIATRIC HEMATOLOGY ONCOLOGY, (JAN-FEB 1998) Vol. 20, No. 1, pp. 1-11.
Publisher: LIPPINCOTT-RAVEN PUBL, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106.
ISSN: 1077-4114.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: CLIN
LANGUAGE: English
REFERENCE COUNT: 179

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Purpose: This review summarizes the molecular genetics of childhood leukemias, with emphasis on pathogenesis and clinical applications.

Design: We first describe the most common genetic events that occur in pediatric acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML). We then illustrate how these molecular alterations may be used to alter therapy.

Results: In childhood ALL, the TEL-AML1 fusion and hyperdiploidy are both associated with excellent treatment outcomes and therefore identify patients who may be candidates for less intensive therapy. In contrast, MLL gene rearrangements and the BCR-ABL fusion confer a poor prognosis; these patients map be best treated by **allogeneic bone marrow** transplantation in first remission.

Conclusions: Although clinical features are important prognostic indicators, genetic alterations of leukemic blasts may be better predictors of outcome for acute leukemia patients. We therefore favor risk-adapted therapy based on classification schemes that incorporate both genetic and clinical features.

L15 ANSWER 20 OF 35 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 97075127 MEDLINE
DOCUMENT NUMBER: 97075127 PubMed ID: 8917553
TITLE: Peptide-specific cytotoxic T lymphocytes restricted by nonself major histocompatibility complex class I molecules: reagents for tumor immunotherapy.
AUTHOR: Sadovnikova E; Stauss H J
CORPORATE SOURCE: Department of Immunology, Royal Postgraduate Medical School, Hammersmith Hospital, London, United Kingdom.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Nov 12) 93 (23) 13114-8.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961230

AB Studies in melanoma patients have revealed that self proteins can function as targets for tumor-reactive cytotoxic T lymphocytes (CTL). One group of self proteins MAGE, BAGE, and GAGE are normally only expressed in testis and placenta, whilst another group of CTL

recognized proteins are melanocyte-specific differentiation antigens. In this study we have investigated whether CTL can be raised against a ubiquitously expressed self protein, **mdm-2**, which is frequently overexpressed in tumors. The observation that T-**cell** tolerance is self major histocompatibility complex-restricted was exploited to generate CTL specific for an **mdm-2** derived peptide presented by nonself major histocompatibility complex class I molecules. Thus, the allo-restricted T-**cell** repertoire of H-2d mice was used to isolate CTL specific for the mdm100 peptide presented by **allogeneic** H-2Kb class I molecules. In vitro, these CTL discriminated between transformed and normal **cells**, killing specifically Kb-positive melanoma and lymphoma tumors but not Kb-expressing dendritic **cells**. In vivo, the CTL showed antitumor activity and delayed the growth of melanoma as well as lymphoma tumors in H-2b recipient mice. These experiments show that it is possible to circumvent T-**cell** tolerance to ubiquitously expressed self antigens, and to target CTL responses against tumors expressing elevated levels of structurally unaltered proteins.

L15 ANSWER 21 OF 35 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 97064184 MEDLINE
DOCUMENT NUMBER: 97064184 PubMed ID: 8906803
TITLE: Impaired signaling in alloantigen-specific CD8+ T **cells** tolerized in vivo: employing a model of Ld-specific TCR **transgenic** mice transplanted with **allogenic** hearts under the cover of a short-term rapamycin treatment.
AUTHOR: Chen H; Luo H; Xu D; Loh D Y; Daloze P M; Veillette A; Qi S; Wu J
CORPORATE SOURCE: Louis-Charles Simard Research Center, Notre-Dame Hospital, University of Montreal, Canada.
SOURCE: JOURNAL OF IMMUNOLOGY, (1996 Nov 15) 157 (10) 4297-308.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20000303
Entered Medline: 19961231

AB Peripheral tolerance of T **cells** is necessary because thymic deletion is not complete, and tissue-specific Ags exist outside the thymus. We have reported that persistent Ag is required to maintain peripheral tolerance in vivo. We suspect that the TCR signaling pathway in in vivo tolerized **cells** is compromised due to continuous exposure to the Ags. In this study, the TCR signaling events in these **cells** were investigated using TCR **transgenic** mice (2C mice) whose T **cells** are predominantly Ld alloantigen-specific CD8 **cells**. The 2C mice were thymectomized and then rendered tolerant to Ld Ag by **allogenic** heart transplantation plus short-term treatment with rapamycin. We found that 1) the in vivo tolerized CD8 **cells** have compromised intracellular Ca2+ flux upon mitogen stimulation; and 2) their cellular tyrosine proteins fail to be

phosphorylated properly upon TCR cross-linking. These results indicate that the signaling pathway in the in vivo tolerized CD8 **cells** is indeed defective. We also found that 1) the tolerized CD8 **cells** have no characteristic surface markers; and 2) the allograft is probably the place where the rejection response is initiated according to the appearance of an early activation marker of T **cells** on graft-infiltrating **cells**.

L15 ANSWER 22 OF 35 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 96281904 MEDLINE
DOCUMENT NUMBER: 96281904 PubMed ID: 8676073
TITLE: Constitutive expression of bcl-2 in B **cells** causes a lethal form of lupuslike autoimmune disease after induction of neonatal tolerance to H-2b alloantigens.
AUTHOR: Lopez-Hoyos M; Carrio R; Merino R; Buelta L; Izui S; Nunez G; Merino J
CORPORATE SOURCE: Department of Immunology, Hospital Universitario M. Valdecilla, Santander, Spain.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1996 Jun 1) 183 (6) 2523-31.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960822
Last Updated on STN: 20000303
Entered Medline: 19960815

AB The bcl-2 protooncogene has been shown to provide a survival signal to self-reactive B **cells**, but it fails to override their developmental arrest after encounter with antigen. Furthermore, constitutive expression of bcl-2 in B **cells** does not promote the development of autoimmune disease in most strains of mice, indicating that signals other than those conferred by bcl-2 are required for long-term survival and differentiation of self-reactive B **cells** in vivo. To further examine the factors that are required for the pathogenesis of autoimmune disease, we have assessed the effect of bcl-2 overexpression on the development of host-versus-graft disease, a self-limited model of systemic autoimmune disease. In this model, injection of spleen **cells** from (C57BL/6 x BALB/c)F1 hybrid mice into BALB/c newborn parental mice induces immunological tolerance to donor tissues and activation of autoreactive F1 donor B **cells** through interactions provided by **allogeneic** host CD4+ T **cells**. BALB/c newborns injected with spleen **cells** from (C57BL/6 x BALB/c)F1 mice expressing a bcl-2 **transgene** in B **cells** developed high levels of anti-single-stranded DNA and a wide range of pathogenic autoantibodies that were not or barely detectable in mice injected with nontransgenic spleen **cells**. In mice injected with **transgenic** B **cells**, the levels of pathogenic autoantibodies remained high during the course of the study and were associated with long-term persistence of donor B **cells**, development of a severe autoimmune disease, and accelerated mortality. These results demonstrate that bcl-2 can provide survival signals for the

maintenance and differentiation of autoreactive B **cells**, and suggest that both increased B **cell** survival and T **cell** help play critical roles in the development of certain forms of systemic autoimmune disease.

L15 ANSWER 23 OF 35 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 95161736 MEDLINE
DOCUMENT NUMBER: 95161736 PubMed ID: 7858247
TITLE: The biology and treatment of acute lymphoblastic leukemia in adults.
AUTHOR: Copelan E A; McGuire E A
CORPORATE SOURCE: Department of Internal Medicine, Ohio State University, Columbus.
CONTRACT NUMBER: 16058 (NIAID)
5-ROA-AI30629-03
SOURCE: BLOOD, (1995 Mar 1) 85 (5) 1151-68. Ref: 212
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950404
Last Updated on STN: 19950404
Entered Medline: 19950322

AB Despite reports to the contrary, only a small minority of adults with ALL are currently cured. Results have improved modestly with more intensive postremission chemotherapy and with tailoring of protocols in individuals with specific subsets of ALL. The use of growth factors may further improve treatment results. The performance of **allogeneic** BMT in first remission is clearly effective in some individuals, eg, those with Ph1-positive ALL, but it is unclear whether it is advantageous in most individuals. There are little data supporting the effectiveness of autotransplantation, as currently performed in ALL, despite its theoretical potential. Advances in understanding the biology of ALL have led to new approaches currently under basic and clinical investigation. These include serial studies of minimal residual disease by a variety of techniques to tailor treatment, the development of conjugated MoAbs to lymphoid **cell** antigens and immunologic and biochemical approaches to chimeric RNA and peptides generated by abnormal fusion genes. It seems likely that substantial improvement in the treatment of adult ALL awaits better characterization of the biology of this disease. However, some improvement will occur through empirical clinical research. It is critical that physicians recognize the poor results with current therapeutic approaches and enter patients into large well-designed clinical trials.

L15 ANSWER 24 OF 35 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95214551 EMBASE
DOCUMENT NUMBER: 1995214551
TITLE: Does purging with antisense make sense?.
AUTHOR: Gewirtz A.M.
CORPORATE SOURCE: John Morgan Building, University of Pennsylvania, School of Medicine, 36th Street and Hamilton

Walk,Philadelphia, PA 19104, United States
SOURCE: Bone Marrow Transplantation, (1995) 15/SUPPL. 1 (S314-S319).
ISSN: 0268-3369 CODEN: BMTRE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 022 Human Genetics
025 Hematology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English

L15 ANSWER 25 OF 35 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 95010272 MEDLINE
DOCUMENT NUMBER: 95010272 PubMed ID: 7925579
TITLE: CD2-CD48 interaction prevents apoptosis in murine B lymphocytes by up-regulating bcl-2 expression.
AUTHOR: Genaro A M; Gonzalo J A; Bosca L; Martinez C
CORPORATE SOURCE: Instituto de Bioquimica Facultad de Farmacia, CSIC, Universidad Complutense, Madrid, Spain.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1994 Oct) 24 (10) 2515-21.
Journal code: EN5; 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19941222
Entered Medline: 19941107

AB Antigen receptor engagement initiates clonal expansion and antibody secretion in B lymphocytes in response to foreign antigens. However, binding of self antigen to antigen receptors targets self-reactive B **cell** clones for elimination or inactivation. The antigen-triggered biochemical events and the eventual response of the **cells** are dependent on the simultaneous occupancy of co-stimulatory receptors. CD2 is an intercellular adhesion molecule implicated in **cell** activation and expressed in human T and natural killer **cells** as well as in mouse B lymphocytes. Mouse B **cells** specific for **allogeneic** major histocompatibility complex (MHC) class I initiate a suicide program that leads to DNA fragmentation and **cell** death when confronted with soluble MHC class I while undergoing clonal expansion when the antigen is present on mitomycin C-treated **cells**. Here we show that occupancy of CD2 in mouse B **cells** by the presence of either monoclonal antibody (mAb) specific for CD2, or soluble recombinant mouse CD48, its natural ligand in mouse, prevents the induction of apoptosis. Furthermore, the in vitro activation by mitomycin C-treated **allogeneic cells**, is abrogated in the presence of anti-CD48 mAb (OX78). These results indicate that a CD2-CD48 interaction is involved in the control of B **cell** activation.

L15 ANSWER 26 OF 35 BIOSIS COPYRIGHT 2002 BIOSIS
ACCESSION NUMBER: 1993:204943 BIOSIS
DOCUMENT NUMBER: PREV199395106168
TITLE: The effect on embryonic development of

micromanipulation techniques used for producing **transgenic** mice.
AUTHOR(S): Andreeva, L. E.; Serova, I. A.
CORPORATE SOURCE: Inst. Mol. Genet., Acad. Sci. Russ., Moscow Russia
SOURCE: Ontogenez, (1992) Vol. 23, No. 6, pp. 637-643.
ISSN: 0475-1450.
DOCUMENT TYPE: Article
LANGUAGE: Russian
SUMMARY LANGUAGE: Russian; English
AB Non-specific effects of micromanipulation techniques used for producing **transgenic** mice on processes of embryonic development were studied. Zygotes obtained from C57BL and BALBxDD mice were treated as follows: (1) incubated in culture medium; (2) the male pronucleus punctured with a glass microneedle; (3) microinjected with a buffer solution; and (4) DNA (mouse P-35 **oncogene** with human insulin gene promotor) injected into the male pronucleus. Then zygotes were transferred into oviducts of syngeneic or **allogeneic** pseudopregnant females. Such treatment resulted in the intrauterine death of embryos, as well as in birth of the dead or non-viable offspring with numerous defects of development. Zygote pronucleus puncturing is the most damaging manipulation, since its effect exceeds that of the zygote incubation and is comparable with the effect of buffer of DNA injections.

L15 ANSWER 27 OF 35 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91282615 EMBASE
DOCUMENT NUMBER: 1991282615
TITLE: Expression of HLA-A2 antigen in human melanoma **cell** lines and its role in T-**cell** recognition.
AUTHOR: Pandolfi F.; Boyle L.A.; Trentin L.; Kurnick J.T.; Isselbacher K.J.; Gattoni-Celli S.
CORPORATE SOURCE: MA General Hosp. Pathlgy. Res., 149 Thirteenth Street,Charlestown, MA 02129, United States
SOURCE: Cancer Research, (1991) 51/12 (3164-3170).
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Previous studies have suggested that, in human melanoma, expression of HLA-A2 antigen is important for tumor **cell** recognition by autologous T-lymphocytes. Because of the recent demonstration that expression of HLA Class I antigens may be selectively lost in several human tumors, including melanoma, we derived pairs of tumor infiltrating lymphocytes (TIL) and melanoma **cell** lines from 4 human lymphocytic antigen (HLA)-A2+ patients with metastatic melanoma. We observed that, although all 4 TIL cultures expressed HLA-A2 antigen, only 2 melanoma **cell** lines did so. Melanoma **cells** derived from the other 2 patients showed neither surface expression of the HLA-A2 antigen nor presence of the corresponding mRNA. We also observed some correlation between loss of HLA-A2 expression and level of **c-myc**

transcription. TIL derived from patients whose melanoma **cell** lines had normal expression of HLA-A2 had a CD8 phenotype and were capable of lysing autologous melanoma **cells**. Melanoma **cell** killing was CD3 and major histocompatibility complex Class I restricted in both cases, but HLA-A2 restricted in only one case. On the other hand, TIL derived from the 2 patients whose melanoma **cell** lines had lost expression of HLA-A2 had a predominant CD4 phenotype and virtually no cytotoxic activity. Preincubation of the HLA-A2 negative melanoma **cell** lines with .alpha.- or .gamma.-interferon did not induce the re-expression of the HLA-A2 antigen. In an attempt to restore HLA-A2 antigen expression in one of the melanoma **cell** lines that were HLA-A2 negative, we transfected these **cells** with the HLA-A2 gene subcloned in the pSV2-neo vector. Four transfected clones, with high levels of HLA-A2 antigen expression, were expanded and characterized. Proliferative and cytotoxic activities of TIL against the autologous transfected clones as well as the untransfected parental melanoma **cell** line were measured and compared. CD4+ TIL showed no difference in the proliferative response to autologous parental and HLA-A2 transfected clones. However, we observed selective recognition of the HLA-A2 expressing clones by autologous cultured peripheral blood lymphocytes (which contained CD8 **cells**) as well as **allogeneic** CD8+ TIL with a HLA-A2 restricted pattern of recognition. In contrast, virtually no cytotoxic activity was detected against either parental or HLA-A2 transfected clones. Overall, our data suggest that selective down-regulation of HLA-A2 antigen expression in melanoma **cells** may represent one of the mechanisms by which tumor **cells** escape immunological recognition.

L15 ANSWER 28 OF 35 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 92008168 MEDLINE
DOCUMENT NUMBER: 92008168 PubMed ID: 1655469
TITLE: A pertussis toxin-sensitive process controls thymocyte emigration.
AUTHOR: Chaffin K E; Perlmutter R M
CORPORATE SOURCE: Howard Hughes Medical Institute, University of Washington, Seattle 98195.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1991 Oct) 21 (10) 2565-73.
Journal code: EN5; 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199111
ENTRY DATE: Entered STN: 19920124
Last Updated on STN: 20000303
Entered Medline: 19911113

AB Although it is well known that essentially all peripheral T **cells** are derived from **bone marrow** progenitors that mature in the thymus, the mechanism whereby thymocytes gain access to peripheral compartments is obscure. We have learned that this process is sensitive to pertussis toxin (PT). **Transgenic** lck-PT mice were generated which express the catalytic subunit of PT in all thymocytes. In a previous study we observed that T **cell** receptor signaling is unimpaired in these **cells** despite the virtual elimination of their Gi

protein signal transduction elements through endogenous PT activity. Here we demonstrate that mature T lineage **cells** accumulate in lck-PT thymuses and fail to populate peripheral lymphoid organs. The accumulating **cells** closely resemble normal peripheral T lymphocytes with respect to **cell** surface phenotype and responses to **allogeneic** spleen **cells**, yet perform poorly in in vivo homing assays. This migratory defect does not result from deficient expression of common homing receptors or alterations in intracellular cAMP concentrations. Based on these results, we propose that a novel PT-sensitive signaling pathway, almost certainly involving a Gi protein, is required for thymocyte emigration.

L15 ANSWER 29 OF 35 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 15

ACCESSION NUMBER: 91099073 EMBASE
DOCUMENT NUMBER: 1991099073
TITLE: Provirus integration at the 3' region of N-myc in **cell** lines established from thymic lymphomas spontaneously formed in AKR mice and a [(BALB/c x B6)F1.rarw.AKR] **bone marrow** chimera.
AUTHOR: Yano Y.; Kobayashi S.; Yasumizu R.; Tamaki J.; Kubo M.; Sasaki A.; Hasan S.; Okuyama H.; Inaba M.; Ikehara S.; Hiai H.; Kakinuma M.
CORPORATE SOURCE: Section of Bacterial Infection, Institute of Immunological Science, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060, Japan
SOURCE: Japanese Journal of Cancer Research, (1991) 82/2 (176-183).
ISSN: 0910-5050 CODEN: JJCREP
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
022 Human Genetics
025 Hematology
047 Virology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Among 18 thymic leukemia **cell** lines which have been established from spontaneous thymic lymphomas in AKR mice as well as in **bone marrow** chimeras which were constructed by transplanting **allogeneic bone marrow** **cells** into irradiated AKR mice, three proviral integration sites were identified; near **c-myc**, N-myc and pim-1 loci. No integration site specific for chimeric leukemia **cell** lines was found. In three thymic leukemia **cell** lines which contained rearranged N-myc genes, insertions of long terminal repeats (LTRs) of murine leukemia viruses were detected at 18 or 20 bp downstream of the translational termination codon. These results demonstrate that the 3' region of the N-myc gene is one of the integration targets for murine leukemia viruses in spontaneous thymic lymphomas. In these three **cell** lines, N-myc mRNA was stably transcribed and transcription of **c-myc** mRNA was down-regulated. The integrated murine leukemia viruses in AKR thymic leukemia were most likely AKV, though the DNA sequence of

the LTR inserted in the genome of a leukemic **cell** line from [(BALB/c x B6)F1.rarw.AKR], CAK20, was different from LTRs of murine leukemia viruses so far reported.

L15 ANSWER 30 OF 35 BIOSIS COPYRIGHT 2002 BIOSIS DUPLICATE 16
ACCESSION NUMBER: 1991:115775 BIOSIS
DOCUMENT NUMBER: BA91:63165
TITLE: CHEMICAL-RETROVIRAL COOPERATIVE CARCINOGENESIS AND ITS MOLECULAR BASIS IN NIH-3T3 **CELLS**.
AUTHOR(S): HASSAN Y; PRIEL E; SEGAL S; HULEIHEL M; ABOUD M
CORPORATE SOURCE: DEP. MICROBIOL., FAC. HEALTH SCI., BEN GURION UNIV. NEGEV, BEER SHEVA, IRAEL.
SOURCE: CARCINOGENESIS (EYNSHAM), (1990) 11 (12), 2097-2102. CODEN: CRNGDP. ISSN: 0143-3334.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB We demonstrate in this study that infection with Moloney murine leukemia virus (M-MLV) and exposure to 3-methylcholanthrene (3-MC) can cooperate to transform NIH/3T3 mouse **fibroblasts**. M-MLV seems to stimulate the expression of **c-myc** and of a certain major histocompatibility complex (MHC) class I gene. Yet M-MLV infection by itself is insufficient to transform these **cells**. However, exposure of the infected **cells** to 3-MC resulted in a rapid **cell** transformation with concomitant enhancement of c-H-ras and H-2K class I MHC gene expression in the transformed **cells**. No such transformation was observed when uninfected NIH/3T3 **cells** were similarly treated with this carcinogen. Clones of **cells** transformed by this combined effect of M-MLV and 3-MC were found to be highly tumorigenic in fully immunocompetent **allogeneic** BALB/c mice. We provide evidence to suggest that the enhanced expression of the H-2K gene in the transformed **cells** plays an important role in overcoming the BALB/c **allogeneic** barrier and allowing tumor growth in these mice.

L15 ANSWER 31 OF 35 CANCERLIT
ACCESSION NUMBER: 90658489 CANCERLIT
DOCUMENT NUMBER: 90658489
TITLE: THE ISOLATION AND CHARACTERIZATION OF GROWTH REGULATORY FACTORS PRODUCED BY A HERPES SIMPLEX VIRUS TYPE 2 TRANSFORMED MOUSE TUMOR **CELL** LINE, H238.
AUTHOR: Stagg R B
CORPORATE SOURCE: Loma Linda Univ.
SOURCE: Diss Abstr Int [B], (1989). Vol. 49, No. 12, pp. 5146.
ISSN: 0419-4217.
DOCUMENT TYPE: (THESIS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199001
AB Transformation of **cells** with herpes simplex virus Type 2 (HSV-2) occurs by an unknown mechanism. No specific gene or gene product has been consistently associated with HSV-2 transformation as is the case for other tumor viruses. This study was performed in an attempt to associate HSV-2-transformation with specific growth factors in order to develop a testable model for HSV-2-transformation. For some tumor viruses, particularly those

containing RNA, there has been a central concept (autocrine secretion) linking **oncogenes** and growth factors. This concept centers on the ability of the cancer **cells** to produce and respond to their own autologous factors. We report here the isolation and characterization of four growth regulatory factors produced by H238, an HSV-2-transformed mouse tumor **cell** line. The H238 **cells** were grown in culture flasks to two-thirds confluency in medium containing 10% fetal bovine serum. The medium was removed, the **cells** were washed and medium without serum was added to the **cells**. At intervals of 48 hr, this conditioned medium (H238-CM), which contained growth regulatory factors, produced by the **cells**, was withdrawn and stored frozen. These factors were separated from the H238-CM by heparin-sepharose affinity chromatography into three peaks of mitogenic activity and a fourth containing inhibitory activity for splenocytes. The three peaks of mitogenic activity have been identified based on physiochemical characteristics: the first supported the anchorage-independent growth of EGF treated NRK-c-49 **cells** and resembles transforming growth factor-beta; the second bound to lectin-coated sepharose beads and was sensitive to trypsin, neuraminidase, and the reducing agent dithiothreitol and, resembled a platelet-derived growth factor-like factor; and the third displaced [125I]-labeled basic **fibroblast** growth factor in a dose dependent fashion when tested with a radioimmune assay. The fourth peak was inhibitory for a variety of splenocyte function assays. It inhibited lectin-induced blastogenesis, **allogenic** mixed lymphocyte reaction, and IL-2 production by splenocytes. It appeared to act on splenocyte G0/G1 transition causing growth arrest by inhibiting **c-myc** proto-**oncogene** expression. A model for the interaction of these factors in vivo is presented with an emphasis on testability. (Full text available from University Microfilms International, Ann Arbor, MI, as Order No. AAD88-14203)

L15 ANSWER 32 OF 35 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 89110163 EMBASE
DOCUMENT NUMBER: 1989110163
TITLE: T **cells** in transplantation immunity.
AUTHOR: Mitchison N.A.
CORPORATE SOURCE: Imperial Cancer Research Fund, Tumour Immunology Unit, Department of Biology, London WC1E 6BT, United Kingdom
SOURCE: Immunology Letters, (1989) 21/1 (15-19).
ISSN: 0165-2478 CODEN: IMLED6
COUNTRY: Netherlands
DOCUMENT TYPE: Journal
FILE SEGMENT: 026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB This paper reviews the following problems in transplantation immunity: (i) short-lived ability to transfer immunity or suppression, in contrast to long-lived immunological memory in the autochthonous animal; (ii) short-lived ability to transfer graft-resistance, in contrast to long-lived ability to transfer helper activity for B-**cells**; (iii) the response to H-Y, as a system that might solve some outstanding problems in **antigen presentation**; and (iv) the contrast between live and killed **allogeneic cells** as

immunogens. All of these problems, it is suggested, are amenable to study by modern methods. Students like me were drawn into Peter Medawar's orbit in the 1940s and 1950s by an irresistible mix of intellectual challenge and the glamour of experimental surgery. Much the same was happening elsewhere in the laboratories of Ray Owen, Milan Hasek, George Snell, Burnet, and Florey, and by 1960 the transplantation immunologists could justly claim to have opened up a whole new area of ideas in biology; we had discovered the lymphocyte as the antigen-sensitive **cell**, and the principles of immunological tolerance; we had revived interest in **cellular** immunity, and it was we who found the MHC (even if we had little idea of its real meaning). But by 1960 the first wave of success had passed, and the penetration of immunology by molecular biology had begun. Interest in transplantation immunity perceptibly declined, although many groups continued to address important problems, particularly in the field of organ transplantation. What brought the change home to me was when a bright young molecular biologist from Strasbourg explained that she longed to use skin grafts to discover how her **transgenic** mice were responding to their foreign MHC molecules (she had placed them under the control of the insulin promoter), but felt that grafting was far too difficult for her! So I take this occasion, before the moment finally passes, to identify four unsolved problems in transplantation immunity that have cropped up in the course of my research. Their status as paradox is a little uncertain for, although a contradiction seems to have arisen, one may not be comparing like with like, But they hint that something interesting is going on, and they are all amenable to study by modern methods.

L15 ANSWER 33 OF 35 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 88330247 MEDLINE
DOCUMENT NUMBER: 88330247 PubMed ID: 3417371
TITLE: **c-myc** expression and transformed phenotypes in hybrid clones between mouse plasmacytoma S194 **cells** and normal spleen **cells** or **fibroblasts**.
AUTHOR: Oikawa T; Yuhki Y; Kondoh N; Abe K; Yuhki N; Ogiso Y; Kuzumaki N
CORPORATE SOURCE: Laboratory of Molecular Genetics, Hokkaido University School of Medicine, Sapporo, Japan.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1988 Sep 15) 42 (3) 435-40.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198810
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19881024

AB Expression of the rearranged **c-myc** **oncogene** and transformed phenotypes was investigated in 2 different types of somatic **cell** hybrid clones between a BALB/c mouse plasmacytoma line (S194) and normal **allogeneic** spleen **cells** or **fibroblasts**. In the parental S194 **cells**, one allele of the **c-myc** was rearranged and its 5'-flanking region was partially deleted by

recombination with the immunoglobulin C alpha gene. Due to this recombination, S194 **cells** expressed approximately 20-fold higher than normal spleen or **fibroblast** levels of **c-myc** transcripts from the rearranged allele, which are smaller than normal germ-line 2.4-kb **c-myc** transcripts, but they expressed the same low levels of 2.4-kb **c-myc** transcripts from the non-rearranged allele as compared with normal spleen **cells** or **fibroblasts**. All the hybrid clones retained both the rearranged and the non-rearranged **c-myc**. The hybrid clones between S194 and normal spleen **cells** showed transformed phenotypes and expressed the same high levels of rearranged **c-myc** transcripts and low levels of the non-rearranged **c-myc** transcripts as the parental S194 **cells**. On the other hand, the hybrid clones between S194 **cells** and normal **fibroblasts** showing non-transformed phenotypes inhibited expression of the rear-ranged **c-myc** to undetectable levels but expressed the non-rearranged **c-myc** transcripts at low levels. A hybrid clone between S194 **cells** and normal **fibroblasts** showing transformed phenotypes also exhibited the same pattern of **c-myc** expression as the non-transformed hybrid clones. These results indicate that expression of the rearranged **c-myc** in S194 mouse plasmacytoma **cells** is modulated in different ways in different components of **cell** lineages, although the correlation between the levels of rearranged **c-myc** transcripts and the transformed phenotypes in the hybrid clones was not absolute.

L15 ANSWER 34 OF 35 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 88083065 MEDLINE
DOCUMENT NUMBER: 88083065 PubMed ID: 3121357
TITLE: Activation of murine CD8+ lymphocytes: two distinct signals regulate **c-myc** and interleukin 2 receptor RNA expression.
AUTHOR: Hardt C
CORPORATE SOURCE: Junior Research Unit, Max-Planck-Institut fur Immunobiologie, Freiburg, FRG.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1987 Dec) 17 (12) 1711-7.
Journal code: EN5; 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198802
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19880220

AB Resting cytotoxic T lymphocyte precursors (CTL-P; CD8+) constitutively express T **cell** receptors (TcR) on their **cell** surfaces. CTL-P are preactivated if binding of the corresponding antigen (mitogens, **allogeneic** major histocompatibility complex (MHC) determinants, viral proteins or haptens in conjunction with self MHC structures) to the TcR takes place. Using a myc-specific probe I show that within 12 h first antigen binding leads to optimal **c-myc** RNA

expression which seems to be the first sign that resting CTL-P are preactivated. Thereafter, **c-myc** RNA expression was remarkably reduced only at day 5. Antigen alone, however, is not sufficient for interleukin 2 receptor (IL2R) RNA expression. A monocyte-derived, soluble mediator termed IL2R-inducing factor (RIF) acts in conjunction with antigen to induced the expression of IL2R RNA and functional IL2R on the **cell** surface. RIF is a 44-kDa heat-labile protein produced by accessory **cells** and its function is restricted to CD8+ lymphocytes. IL2R RNA is first expressed 12 h after onset of culture, maximally expressed on day 3 and it decreases thereafter. **Cells** kept in long-term culture without mitogen but in the presence of IL2 do not express high amounts of IL2R RNA. Expression of IL2R RNA can be very efficiently reinduced, however, by mitogenic stimulation. In contrast to primary cultures, IL2R RNA expression peaks earlier and is independent of RIF. The results obtained here show that (a) for CD8+ lymphocytes of primary cultures two distinct activation signals (mitogen and RIF) are necessary for **c-myc** and IL2R RNA expression and (b) for CD8+ lymphocytes of secondary cultures the mitogenic signal alone is sufficient for re-expression of IL2R RNA.

L15 ANSWER 35 OF 35 CANCERLIT
ACCESSION NUMBER: 85615449 CANCERLIT
DOCUMENT NUMBER: 85615449
TITLE: GENETIC AND PHENOTYPIC MARKERS OF TUMORS.
AUTHOR: Anonymous
CORPORATE SOURCE: No affiliation given.
SOURCE: Non-serial, (1984). Genetic and Phenotypic Markers of Tumors. Aaronson SA, Frati L, Verna R, eds. New York, Plenum Press, 379.
DOCUMENT TYPE: Book; (MONOGRAPH)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 198511
AB Chapter titles in this book on genetic and phenotypic markers of tumors are the following: phenotypic and genetic markers of cancer: turning point in research; multiple biochemical markers for cancer: a statistical approach; pseudouridine: a biochemical marker for cancer; serum lipid-associated sialic acid in different human malignancies; preliminary results; heterogeneity of binding sites for triphenylethylene antiestrogens in estrogen target tissues; failure to demonstrate plasma hormone abnormalities in women with operable breast cancer; **cell**-type-independent accumulation of phosphatidic acid induced by trifluoperazine in stimulated human platelets, leukocytes, and **fibroblasts**; protease inhibitors in 3T3 **cells**; heterogeneity of extramitochondrial forms of aspartate aminotransferase and malate dehydrogenase in Yoshida ascites hepatoma; biology and immunology of human carcinoma **cell** populations; monoclonal antibodies against breast cancer; generation of monoclonal antibodies reactive with colon carcinomas; reactivity of cultured mouse natural killer (NK) **cells** against normal non-neoplastic **cells**; modulating effects of thymic factor on natural **cell** -mediated reactivities of natural and cyclophosphamide-treated mice; effect of inactivated Candida albicans on NK **cell** activity and blastogenesis in mice; antitumor adjuvants from C albicans: effects on human **allogeneic** T-**cell** responses 'in

vitro'; interleukin-2 and lymphocytes from tumor bearing mice: a combinatory immunotherapy of tumors; hyporesponsiveness of NK activity induced in vivo by multiple treatment with maleic acid anhydride divinyl ether (MVE-2); Epstein-Barr virus markers in nasopharyngeal carcinoma; interferon-mediated regulation of the NK target structures of normal or lymphoma **cells**; membrane changes induced by interferons in human neoplastic **cells**; modulation of Ia antigens by interferons in human lymphoid **cells**; role of PGE2 produced by neoplastic **cells** as modulators of macrophage chemotaxis; the relationships between the high production of prostaglandins by tumors and their action on lymphocytes as suppressive agents; **oncogenes** and the neoplastic process; modulation of thyroid epithelial differentiation by two viral **oncogenes**; thyroid neoplastic transformation in vitro and in vivo; immunological detection of cellular targets for V-onc gene-coded tyrosine kinases; nucleotide sequences homologous to a cloned repeated human DNA fragment in human leukemic DNAs; rearrangement and abnormal expression of human **c-myc** in acute lymphocytic leukemia; a new human erythroleukemic line: initial characterization and hemin-induced erythroid differentiation; presence of **oncogenes** in spontaneous rat tumors; molecular biology of human T-**cell** leukemia/lymphoma virus (HTLV); high level transcription of a human gene in HTLV-positive T-**cells**: complementary DNA cloning and characterization; and clinical features of HTLV-associated T-**cell** neoplasms.

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